(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 October 2006 (12.10.2006)

PCT

(10) International Publication Number
WO 2006/107853 A2

(51) International Patent Classification:
A61K 31/4745 (2006.01) *C07D 471/02* (2006.01)

(21) International Application Number:
PCT/US2006/012265

(22) International Filing Date: 31 March 2006 (31.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/667,828 1 April 2005 (01.04.2005) US

(71) Applicant *(for all designated States except US)*: **3M INNOVATIVE PROPERTIES COMPANY** [US/US]; 3M Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HAYS, David, S.** [US/US]; 3M Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **NIWAS, Shri** [US/US]; 3M Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **LUNDQUIST, Gregory, D., Jr.** [US/US]; 3M Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US).

(74) Agents: **ERSFELD, Dean, A.** et al.; 3M Center, Office Of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PYRAZOLOPYRIDINE-1,4-DIAMINES AND ANALOGS THEREOF

(57) Abstract: Pyrazolopyridine-1,4-diamines and analogs thereof, e.g., pyrazolo[3,4-*c*]pyridine-1,4-diamines, pyrazolo[3,4-*c*]quinoline-1,4-diamines, 6,7,8,9-tetrahydro pyrazolo[3,4-*c*]quinoline-1,4-diamines, and pyrazolo[3,4-*c*]naphthyridine-1,4-diamines, pharmaceutical compositions containing the compounds, intermediates, methods of making these compounds, and methods of use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.

WO 2006/107853 A2

PYRAZOLOPYRIDINE-1,4-DIAMINES AND ANALOGS THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

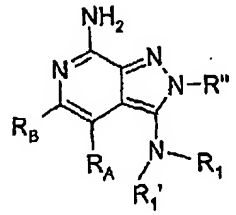
The present invention claims priority to U.S. Provisional Application Serial No. 60/667,828, filed April 1, 2005, which is incorporated herein by reference.

BACKGROUND

Certain compounds have been found to be useful as immune response modifiers (IRMs), rendering them useful in the treatment of a variety of disorders. However, there continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other means.

SUMMARY

The present invention provides a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Such compounds are of the following Formula I:



I

wherein R_A, R_B, R_1, R_1', and R" are as defined below.

The compounds of Formula I are useful as immune response modifiers due to their ability to induce cytokine biosynthesis (e.g., induces the synthesis of at least one cytokine) and otherwise modulate the immune response when administered to animals. This makes the compounds useful in the treatment of a variety of conditions such as viral diseases and tumors that are responsive to such changes in the immune response.

The invention further provides pharmaceutical compositions containing an effective amount of a compound of Formula I and methods of inducing cytokine

biosynthesis in an animal, treating a viral infection or disease and/or treating a neoplastic disease in an animal by administering an effective amount of a compound of Formula I to the animal.

In addition, methods of synthesizing compounds of Formula I and intermediates useful in the synthesis of these compounds are provided.

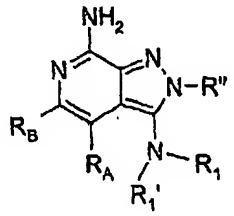
As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the description, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

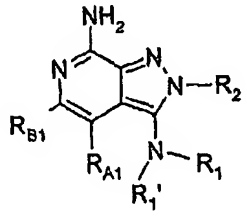
DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides compounds of the following Formula I:

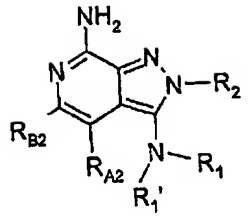


I

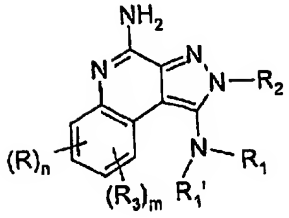
and more specifically compounds of the following Formulas II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, and XVI:



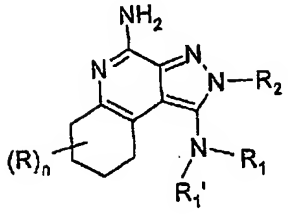
II



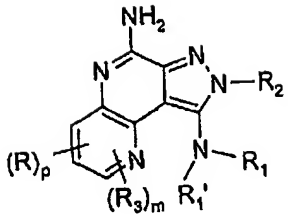
III



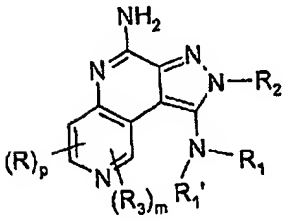
IV



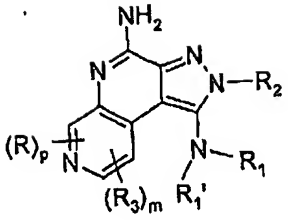
V



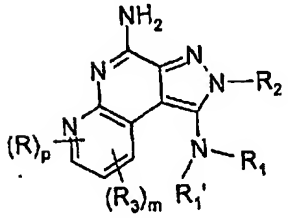
VI



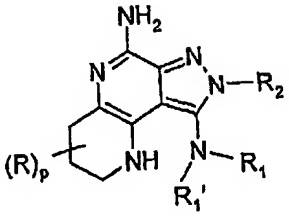
VII



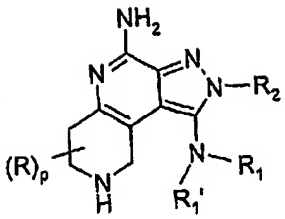
VIII



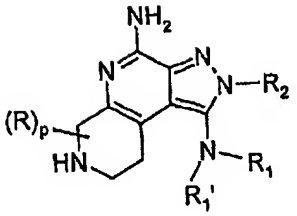
IX



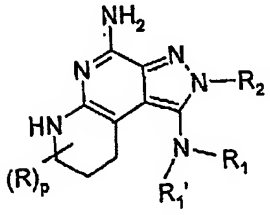
X



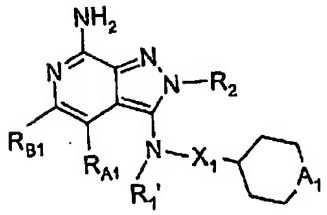
XI



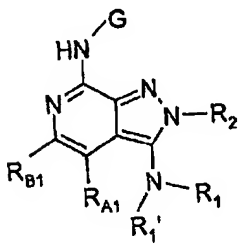
XII



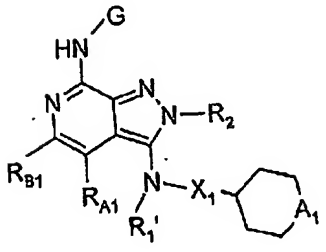
XIII



XIV



XV

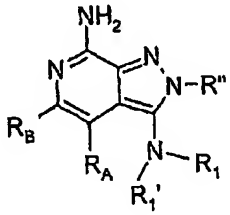


XVI

wherein R_A, R_B, R_{A1}, R_{B1}, R_{A2}, R_{B2}, R, R_1, R_1', R", R_2, R_3, X_1, A_1, G, m, n, and p are as defined below; and pharmaceutically acceptable salts thereof.

In one embodiment, the present invention provides a compound of the Formula I:

wherein:



I

R_1 is selected from the group consisting of:

$-R_4$,

$-Y-R_4$,

$-X-N(R_8)-Y-R_4$,

$-X-C(R_6)-N(R_8)-R_4$,

$-X-O-C(R_6)-N(R_8)-R_4$,

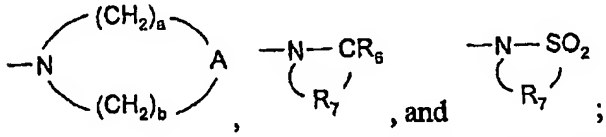
$-X-S(O)_2-N(R_8)-R_4$,

$-X-O-R_4$, and

$-X-R_5$;

R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

or R_1 and R_1' together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:

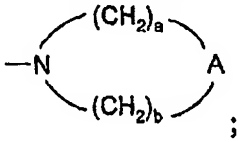


, and ;

A is selected from the group consisting of $-CH(R_8)-$, $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, and $-N(X-N(R_8)-Y-R_4)-$;

X is C_{2-20} alkylene;

Y is selected from the group consisting of $-C(R_6)-$, $-C(R_6)-O-$, $-S(O)_2-$,

$-S(O)_2-N(R_8)-$, and $-C(R_6)-N(R_{11})-$; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group 

;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, $-N(R_8)-$, $-N(Y-R_4)-$, or $-N(X-N(R_8)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

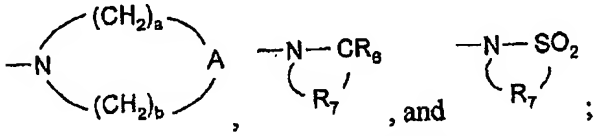
alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, and R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

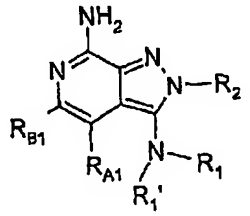
R_9 is selected from the group consisting of hydrogen and alkyl;

R' is a non-interfering substituent; and

R" is hydrogen or a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the Formula II:



II

wherein:

R_1 is selected from the group consisting of:

$-R_4$,

$-Y-R_4$,

$-X-N(R_8)-Y-R_4$,

$-X-C(R_6)-N(R_8)-R_4$,

$-X-O-C(R_6)-N(R_8)-R_4$,

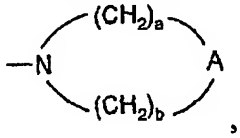
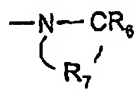
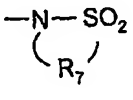
$-X-S(O)_2-N(R_8)-R_4$,

$-X-O-R_4$, and

$-X-R_5$;

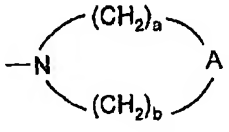
R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

or R_1 and R_1' together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:


, 
, and 
;

A is selected from the group consisting of $-CH(R_8)-$, $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, and $-N(X-N(R_8)-Y-R_4)-$;

X is C_{2-20} alkylene;

Y is selected from the group consisting of $-C(R_6)-$, $-C(R_6)-O-$, $-S(O)_2-$, $-S(O)_2-N(R_8)-$, and $-C(R_6)-N(R_{11})-$; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group 
;

a and b are independently integers from 1 to 4 with the proviso that when A is $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, or $-N(X-N(R_8)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4'$,
$-X'-R_4'$,
$-X'-Y'-R_4'$, and
$-X'-R_5'$;

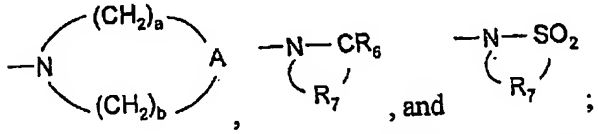
R_3 is selected from the group consisting of:

$-Z-R_4'$,
$-Z-X'-R_4'$,
$-Z-X'-Y'-R_4'$,
$-Z-X'-Y'-X'-Y'-R_4'$, and
$-Z-X'-R_5'$;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, and R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

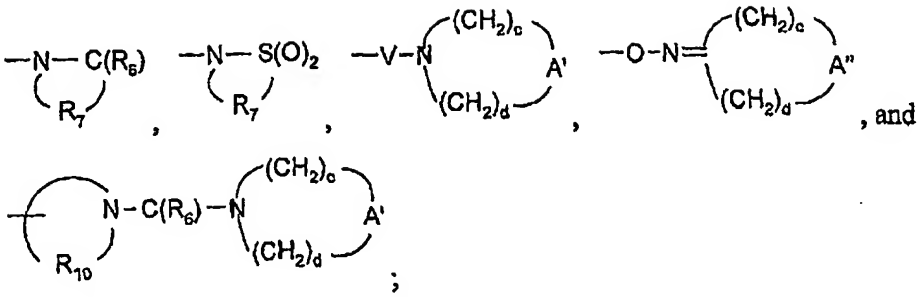
R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_5' is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A' is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, and $-N(R_4)$-;

A" is selected from the group consisting of -O-, $-S(O)_{0-2}$-, $-N(-Q-R_4)$-, and $-CH_2$-;

Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, $-C(R_6)-S$-, and $-C(R_6)-N(OR_9)$-;

V is selected from the group consisting of $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-O-,

$-S(O)_{0-2}$-,

$-S(O)_2-N(R_8)$-,

$-C(R_6)$-,

$-C(R_6)-O$-,

$-O-C(R_6)$-,

-O-C(O)-O-,

$-N(R_8)-Q$-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

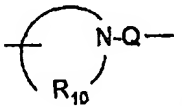
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

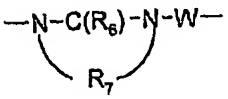
-O-N=C(R_4)-,

-C(=N-O-R_8)-,

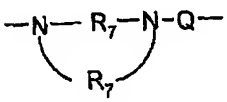
-CH(-N(-O-R_8)-Q-R_4)-,



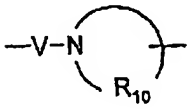
,



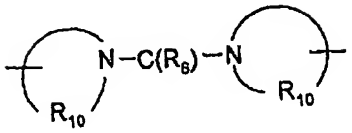
,



,



, and



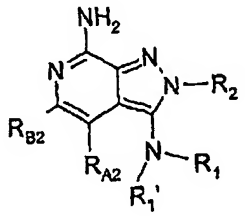
;

Z is a bond or -O-; and

c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the Formula III:



III

wherein:

R_1 is selected from the group consisting of:

$-R_4$,

$-Y-R_4$,

$-X-N(R_8)-Y-R_4$,

$-X-C(R_6)-N(R_8)-R_4$,

$-X-O-C(R_6)-N(R_8)-R_4$,

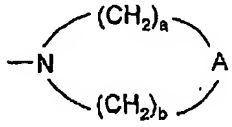
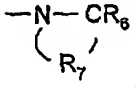
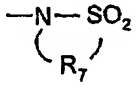
$-X-S(O)_2-N(R_8)-R_4$,

$-X-O-R_4$, and

$-X-R_5$;

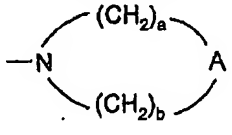
R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

or R_1 and R_1' together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:


, 
, and 
;

A is selected from the group consisting of $-CH(R_8)-$, $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, and $-N(X-N(R_8)-Y-R_4)-$;

X is C_{2-20} alkylene;

Y is selected from the group consisting of $-C(R_6)-$, $-C(R_6)-O-$, $-S(O)_2-$, $-S(O)_2-N(R_8)-$, and $-C(R_6)-N(R_{11})-$; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group 
;

a and b are independently integers from 1 to 4 with the proviso that when A is $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, or $-N(X-N(R_8)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

R_{A2} and R_{B2} are each independently selected from the group consisting of:

hydrogen,

halogen,

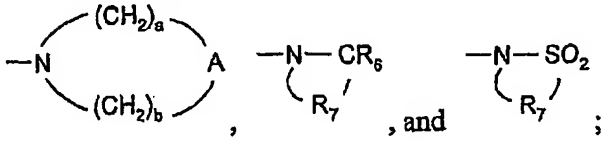
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_2 is selected from the group consisting of:
$-R_4'$,
$-X'-R_4'$,
$-X'-Y'-R_4'$, and
$-X'-R_5'$;

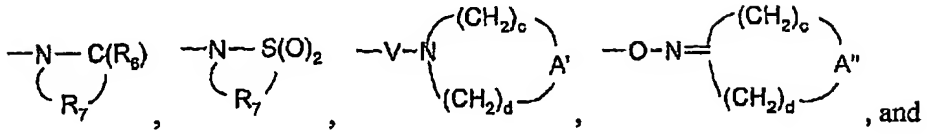
R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, and R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

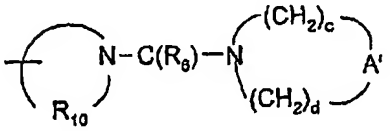
R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_5' is selected from the group consisting of:





;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A' is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A" is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

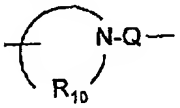
Y' is selected from the group consisting of:

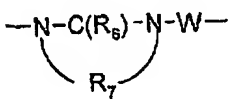
-O-,

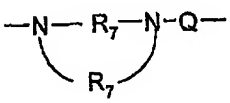
$-S(O)_{0-2}-$,

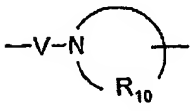
$-S(O)_2-N(R_8)-$,

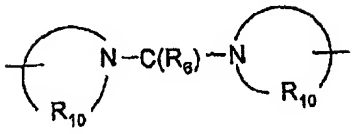
-C(R_6)-,
-C(R_6)-O-,
-O-C(R_6)-,
-O-C(O)-O-,
-N(R_8)-Q-,
-C(R_6)-N(R_8)-,
-O-C(R_6)-N(R_8)-,
-C(R_6)-N(OR_9)-,
-O-N(R_8)-Q-,
-O-N=C(R_4)-,
-C(=N-O-R_8)-,
-CH(-N(-O-R_8)-Q-R_4)-,


,


,


,

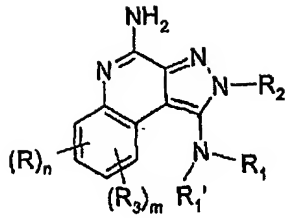

, and


; and

c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the Formula IV:



IV

wherein:

R_1 is selected from the group consisting of:

$-R_4$,

$-Y-R_4$,

$-X-N(R_8)-Y-R_4$,

$-X-C(R_6)-N(R_8)-R_4$,

$-X-O-C(R_6)-N(R_8)-R_4$,

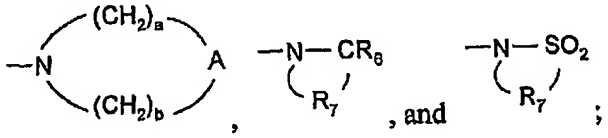
$-X-S(O)_2-N(R_8)-R_4$,

$-X-O-R_4$, and

$-X-R_5$;

R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

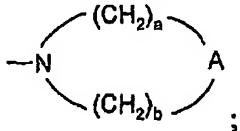
or R_1 and R_1' together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



A is selected from the group consisting of $-CH(R_8)-$, $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, and $-N(X-N(R_8)-Y-R_4)-$;

X is C_{2-20} alkylene;

Y is selected from the group consisting of $-C(R_6)-$, $-C(R_6)-O-$, $-S(O)_2-$,

$-S(O)_2-N(R_8)-$, and $-C(R_6)-N(R_{11})-$; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group 

;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, $-N(R_8)-$, $-N(Y-R_4)-$, or $-N(X-N(R_8)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

n is an integer from 0 to 4;

R_2 is selected from the group consisting of:

$-R_4'$,

$-X'-R_4'$,

$-X'-Y'-R_4'$, and

$-X'-R_5'$;

R_3 is selected from the group consisting of:

$-Z-R_4'$,

$-Z-X'-R_4'$,

$-Z-X'-Y'-R_4'$,

$-Z-X'-Y'-X'-Y'-R_4'$, and

$-Z-X'-R_5'$;

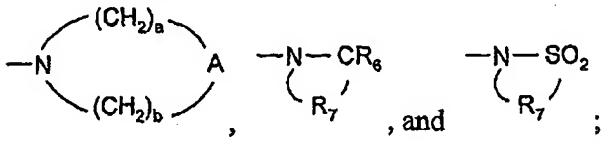
m is 0 or 1 with the proviso that when m is 1 then n is 0 or 1;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and

heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, and R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

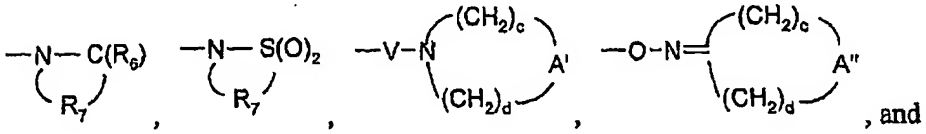
R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

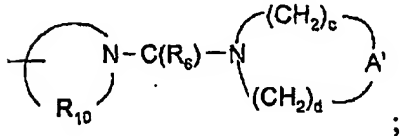
R_5 is selected from the group consisting of:



;

R_5' is selected from the group consisting of:





;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A' is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, and -$N(R_4)$-;

A" is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and -$S(O)_2$-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

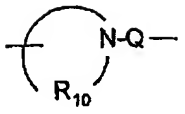
-$C(R_6)$-$N(OR_9)$-,

-O-$N(R_8)$-Q-,

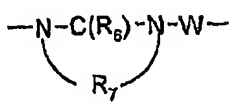
-O-N=$C(R_4)$-,

-C(=N-O-R_8)-,

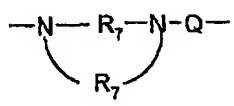
-CH(-N(-O-R_8)-Q-R_4)-,



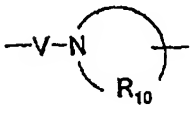
,



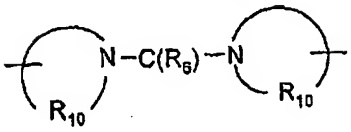
,



,



, and



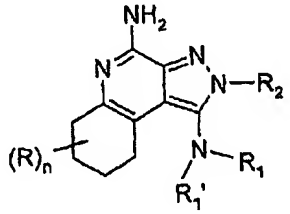
;

Z is a bond or -O-; and

c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the Formula V:



V

wherein:

R_1 is selected from the group consisting of:

$-R_4$,

$-Y-R_4$,

$-X-N(R_8)-Y-R_4$,

$-X-C(R_6)-N(R_8)-R_4$,

$-X-O-C(R_6)-N(R_8)-R_4$,

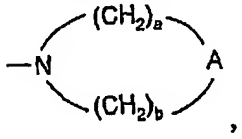
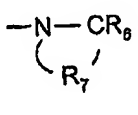
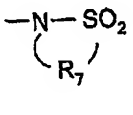
$-X-S(O)_2-N(R_8)-R_4$,

$-X-O-R_4$, and

-X-R_5;

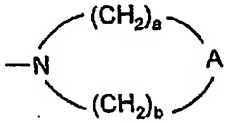
R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

or R_1 and R_1' together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:


, 
, and 
;

A is selected from the group consisting of -CH(R_8)-, -O-, -N(R_8)-, -N(Y-R_4)-, and -N(X-N(R_8)-Y-R_4)-;

X is $C_{2\text{-}20}$ alkylene;

Y is selected from the group consisting of -C(R_6)-, -C(R_6)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_8)-, and -C(R_6)-N(R_{11})-; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group 
;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -N(R_8)-, -N(Y-R_4)-, or -N(X-N(R_8)-Y-R_4)- then a and b are independently integers from 2 to 4;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

n is an integer from 0 to 4;

R_2 is selected from the group consisting of:

$-R_4'$,

$-X'-R_4'$,

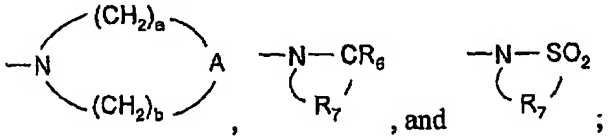
$-X'-Y'-R_4'$, and

$-X'-R_5'$;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, and R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

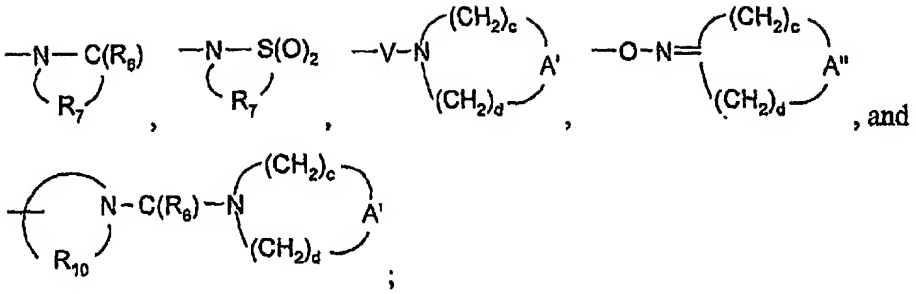
R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



, , and ;

R_5' is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A' is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, and $-N(R_4)$-;

A" is selected from the group consisting of -O-, $-S(O)_{0-2}$-, $-N(-Q-R_4)$-, and $-CH_2$-;

Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, $-C(R_6)-S$-, and $-C(R_6)-N(OR_9)$-;

V is selected from the group consisting of $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-O-,

$-S(O)_{0-2}$-,

$-S(O)_2-N(R_8)$-,

$-C(R_6)$-,

$-C(R_6)-O$-,

$-O-C(R_6)$-,

-O-C(O)-O-,

$-N(R_8)-Q$-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

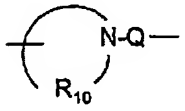
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

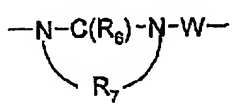
-O-N=C(R_4)-,

-C(=N-O-R_8)-,

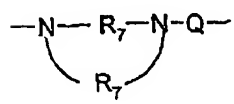
-CH(-N(-O-R_8)-Q-R_4)-,



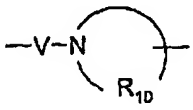
,



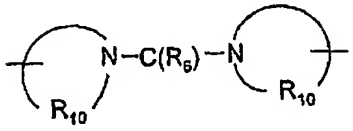
,



,



, and

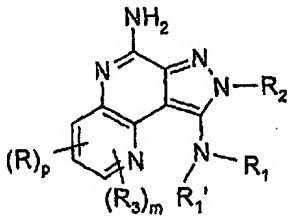


; and

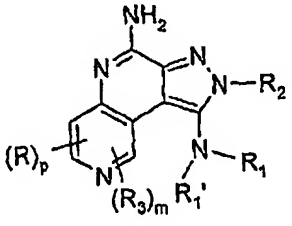
c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7;

or a pharmaceutically acceptable salt thereof.

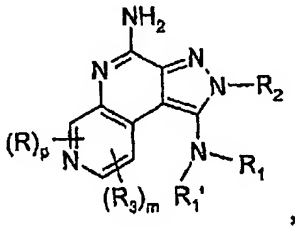
In another embodiment, the present invention provides a compound selected from the group consisting of the Formulas VI, VII, VIII, and IX:



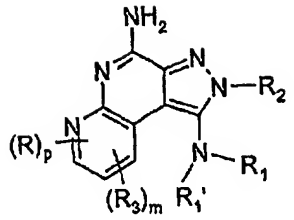
VI



VII



VIII



IX

wherein:

R_1 is selected from the group consisting of:

$-R_4$,

$-Y-R_4$,

$-X-N(R_8)-Y-R_4$,

$-X-C(R_6)-N(R_8)-R_4$,

$-X-O-C(R_6)-N(R_8)-R_4$,

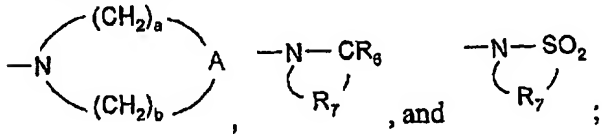
$-X-S(O)_2-N(R_8)-R_4$,

$-X-O-R_4$, and

$-X-R_5$;

R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

or R_1 and R_1' together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:

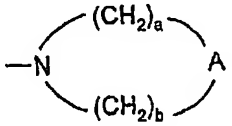


;

A is selected from the group consisting of $-CH(R_8)-$, $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, and $-N(X-N(R_8)-Y-R_4)-$;

X is C_{2-20} alkylene;

Y is selected from the group consisting of $-C(R_6)-$, $-C(R_6)-O-$, $-S(O)_2-$,

$-S(O)_2-N(R_8)-$, and $-C(R_6)-N(R_{11})-$; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group  ;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, $-N(R_8)-$, $-N(Y-R_4)-$, or $-N(X-N(R_8)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

p is an integer from 0 to 3;

R_2 is selected from the group consisting of:

$-R_4'$,

$-X'-R_4'$,

$-X'-Y'-R_4'$, and

$-X'-R_5'$;

R_3 is selected from the group consisting of:

$-Z-R_4'$,

$-Z-X'-R_4'$,

$-Z-X'-Y'-R_4'$,

$-Z-X'-Y'-X'-Y'-R_4'$, and

$-Z-X'-R_5'$;

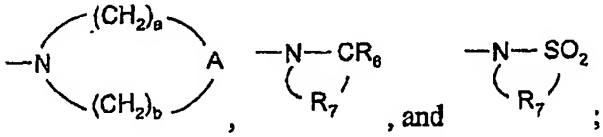
m is 0 or 1 with the proviso that when m is 1 then p is 0 or 1;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and

heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, and R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

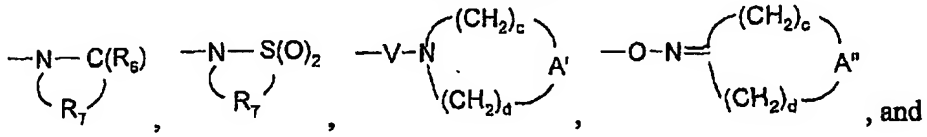
R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

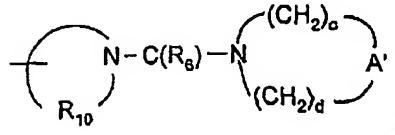


;

R_5' is selected from the group consisting of:



, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A' is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, and -$N(R_4)$-;

A" is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and -$S(O)_2$-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

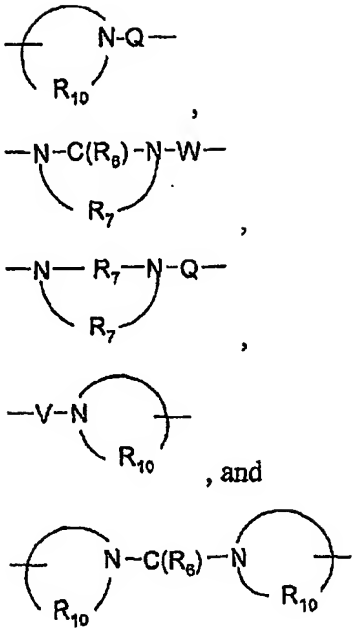
-$C(R_6)$-$N(OR_9)$-,

-O-$N(R_8)$-Q-,

-O-N=$C(R_4)$-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,



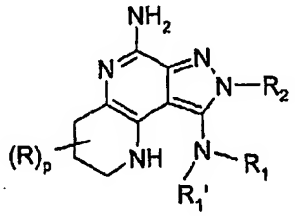
;

Z is a bond or -O-; and

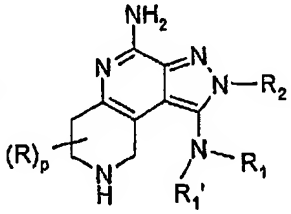
c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7;

or a pharmaceutically acceptable salt thereof.

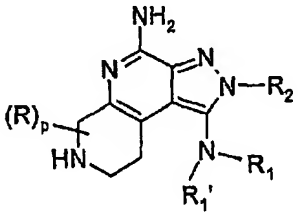
In another embodiment, the present invention provides a compound selected from the group consisting of the Formulas X, XI, XII, and XIII:



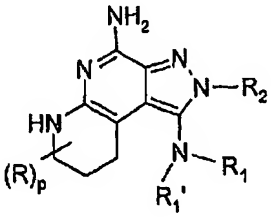
X



XI



XII



XIII

wherein:

R_1 is selected from the group consisting of:

$-R_4$,

-Y-R_4,

-X-N(R_8)-Y-R_4,

-X-C(R_6)-N(R_8)-R_4,

-X-O-C(R_6)-N(R_8)-R_4,

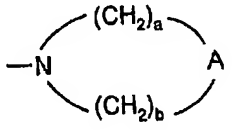
-X-S(O)$_2$-N(R_8)-R_4,

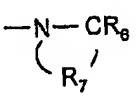
-X-O-R_4, and

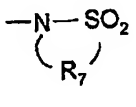
-X-R_5;

R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

or R_1 and R_1' together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



,


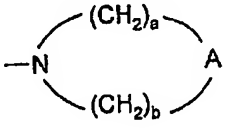
, and


;

A is selected from the group consisting of -CH(R_8)-, -O-, -N(R_8)-, -N(Y-R_4)-, and -N(X-N(R_8)-Y-R_4)-;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -C(R_6)-, -C(R_6)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_8)-, and -C(R_6)-N(R_{11})-; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which



R_{11} is bonded can join to form the group ;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -N(R_8)-, -N(Y-R_4)-, or -N(X-N(R_8)-Y-R_4)- then a and b are independently integers from 2 to 4;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

p is an integer from 0 to 3;

R_2 is selected from the group consisting of:

$-R_4'$,

$-X'-R_4'$,

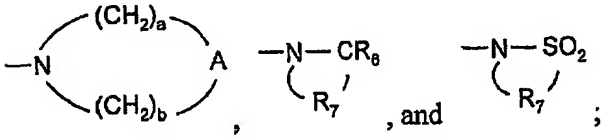
$-X'-Y'-R_4'$, and

$-X'-R_5'$;

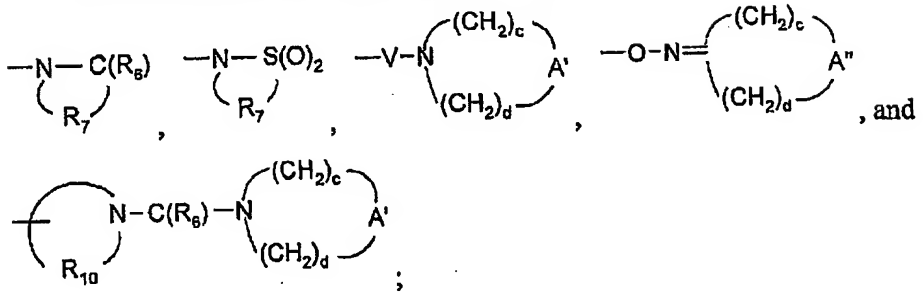
R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl; oxo, with the proviso that when R_1 is R_4, and R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_5' is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A' is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, and $-N(R_4)$-;

A" is selected from the group consisting of -O-, $-S(O)_{0-2}$-, $-N(-Q-R_4)$-, and $-CH_2$-;

Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, $-C(R_6)-S$-, and $-C(R_6)-N(OR_9)$-;

V is selected from the group consisting of $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

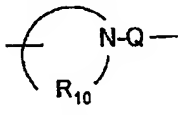
Y' is selected from the group consisting of:

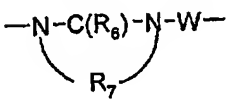
-O-,

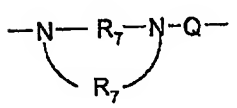
$-S(O)_{0-2}$-,

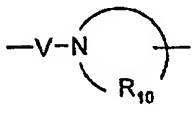
$-S(O)_2-N(R_8)$-,

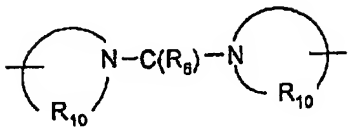
-C(R_6)-,
-C(R_6)-O-,
-O-C(R_6)-,
-O-C(O)-O-,
-N(R_8)-Q-,
-C(R_6)-N(R_8)-,
-O-C(R_6)-N(R_8)-,
-C(R_6)-N(OR_9)-,
-O-N(R_8)-Q-,
-O-N=C(R_4)-,
-C(=N-O-R_8)-,
-CH(-N(-O-R_8)-Q-R_4)-,


,


,


,

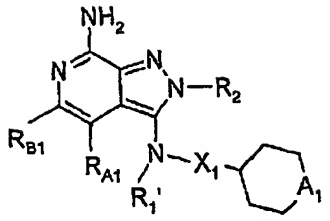

, and


; and

c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the Formula XIV:

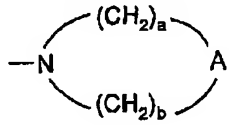


XIV

wherein:

X_1 is a bond or C_{1-4} alkylene;

A_1 is selected from the group consisting of $-N(R_8)-$ and $-N(-Y-R_4)-$;

Y is selected from the group consisting of $-C(R_6)-$, $-C(R_6)-O-$, $-S(O)_2-$, $-S(O)_2-N(R_8)-$, and $-C(R_6)-N(R_{11})-$; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group  ;

A is selected from the group consisting of $-CH(R_8)-$, $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, and $-N(X-N(R_8)-Y-R_4)-$;

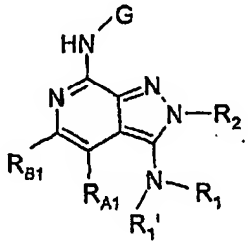
a and b are independently integers from 1 to 4 with the proviso that when A is $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, or $-N(X-N(R_8)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

X is C_{2-20} alkylene; and

R_1', R_2, R_4, R_6, R_8, R_{A1} and R_{B1} are defined as in Formula II above;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the Formula XV:



XV

wherein:

G is selected from the group consisting of:

-C(O)-R'",

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R'",

-C(O)-N(R'"")R'",

-C(=NY$_2$)-R'",

-CH(OH)-C(O)-OY$_2$,

-CH(OC$_{1-4}$ alkyl)Y$_0$,

-CH$_2$Y$_1$, and

-CH(CH$_3$)Y$_1$;

R'" and R"" are independently selected from the group consisting of C$_{1-10}$ alkyl, C$_{3-7}$ cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C$_{1-6}$ alkyl, C$_{1-4}$ alkoxy, aryl, heteroaryl, aryl-C$_{1-4}$ alkylenyl, heteroaryl-C$_{1-4}$ alkylenyl, halo-C$_{1-4}$ alkylenyl, halo-C$_{1-4}$ alkoxy, -O-C(O)-CH$_3$, -C(O)-O-CH$_3$, -C(O)-NH$_2$, -O-CH$_2$-C(O)-NH$_2$, -NH$_2$, and –S(O)$_2$-NH$_2$, with the proviso that R"" can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y$_2$ is selected from the group consisting of hydrogen, C$_{1-6}$ alkyl, and benzyl;

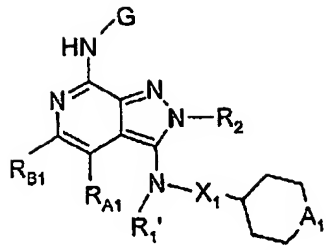
Y$_0$ is selected from the group consisting of C$_{1-6}$ alkyl, carboxy-C$_{1-6}$ alkylenyl, amino-C$_{1-4}$ alkylenyl, mono-*N*-C$_{1-6}$ alkylamino-C$_{1-4}$ alkylenyl, and di-*N*,*N*-C$_{1-6}$ alkylamino-C$_{1-4}$ alkylenyl;

Y$_1$ is selected from the group consisting of mono-*N*-C$_{1-6}$ alkylamino, di-*N*,*N*-C$_{1-6}$ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C$_{1-4}$ alkylpiperazin-1-yl; and

R$_1$, R$_1$', R$_2$, R$_{A1}$, and R$_{B1}$, are defined as in Formula II above;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the Formula XVI:



XVI

wherein:

G is defined as in Formula XV above; and

X_1, A_1, R_1', R_2, R_{A1}, and R_{B1}, are defined as in Formula XIV above;

or a pharmaceutically acceptable salt thereof.

Herein, "non-interfering" means that the ability of the compound or salt, which contains a non-interfering substituent, to modulate (e.g., induce) the biosynthesis of one or more cytokines is not destroyed by the non-interfering substitutent. Illustrative non-interfering R' groups include those described herein for R and R_3. Illustrative non-interfering R" groups include those described herein for R_2.

As used herein, the terms "alkyl", "alkenyl", "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, e.g., cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene", "alkenylene", and "alkynylene" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. The terms, "alkylenyl", "alkenylenyl", and "alkynylenyl" are used when "alkylene", "alkenylene", and "alkynylene", respectively, are substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). In some embodiments, the term "heteroaryl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. In some embodiments, the term "heterocyclyl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heterocyclyl groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), 1,4-oxazepanyl, homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, azetidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, 3-azabicyclo[3.2.2]non-3-yl, and the like.

The term "heterocyclyl" includes bicyclic and tricyclic heterocyclic ring systems. Such ring systems include fused and/or bridged rings and spiro rings. Fused rings can include, in addition to a saturated or partially saturated ring, an aromatic ring, for example,

a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

The terms "arylene", "heteroarylene", and "heterocyclylene" are the divalent forms of the "aryl", "heteroaryl", and "heterocyclyl" groups defined above. The terms, "arylenyl", "heteroarylenyl", and "heterocyclylenyl" are used when "arylene", "heteroarylene", and "heterocyclylene", respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

The term "fused aryl ring" includes fused carbocyclic aromatic rings or ring systems. Examples of fused aryl rings include benzo, naphtho, fluoreno, and indeno.

The term "fused heteroaryl ring" includes the fused forms of 5 or 6 membered aromatic rings that contain one heteroatom selected from S and N.

The term "fused 5 to 7 membered saturated ring" includes rings which are fully saturated except for the bond where the ring is fused.

When a group (or substituent or variable) is present more than once in any formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula $-N(R_9)_2$ each R_9 group is independently selected. In another example, when an R_2 and an R_3 group are both present and each contains a Y' group, and each Y' group contains an R_8 group, each Y' group is independently selected, and each R_8 group is independently selected.

The invention is inclusive of the compounds described herein and salts thereof, in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), solvates, polymorphs, prodrugs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" or the term "compounds" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

The term "prodrug" means a compound that can be transformed in vivo to yield an immune response modifying compound, including any of the salt, solvated, polymorphic, or isomeric forms described above. The prodrug, itself, may be an immune response modifying compound, including any of the salt, solvated, polymorphic, or isomeric forms described above. The transformation may occur by various mechanisms, such as through a chemical (e.g., solvolysis or hydrolysis, for example, in the blood) or enzymatic

biotransformation. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A. C. S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of the present invention contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as C_{1-8} alkyl, C_{2-12} alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-C_{1-2} alkylaminoC_{2-3} alkyl (such as β-dimethylaminoethyl), carbamoyl-C_{1-2} alkyl, N,N-diC_{1-2} alkylcarbamoyl-C_{1-2} alkyl and piperidino-, pyrolidino-, or morpholinoC_{2-3} alkyl.

If a compound of the present invention contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as C_{1-6} alkanoyloxymethyl, 1-(C_{1-6} alkanoyloxy)ethyl, 1-methyl-1-(C_{1-6} alkanoyloxy)ethyl, C_{1-6} alkoxycarbonyloxymethyl, N-(C_{1-6} alkoxycarbonyl)aminomethyl, succinoyl, C_{1-6} alkanoyl, α-aminoC_{1-4} alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $P(O)(O\text{-}C_{1-6}\text{ alkyl})_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

A prodrug of a compound of the present invention can also be formed by the replacement of a hydrogen atom in the amino group at the 4-position (and/or in an amino group at another position) with a group such as R'''-carbonyl, R'''-O-carbonyl, N(R'''')(R''')-carbonyl, -C(=NY_2)-R''', where R''' and R'''' are each independently C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, or 2-phenylethyl, α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(OH)C(O)OY_2 wherein Y_2 is H, C_{1-6} alkyl or benzyl, -C(OY_4)Y_0 wherein Y_4 is C_{1-4} alkyl and Y_0 is C_{1-6} alkyl, carboxyC_{1-6} alkyl, aminoC_{1-4} alkyl or mono-N- or di-N,N-

C_{1-6} alkylaminoC_{1-4} alkyl, $-C(Y_5)Y_1$ wherein Y_5 is H or methyl and Y_1 is mon-N- or di-N,N-C_{1-6} alkylamino, morpholino, piperidin-1-yl, pyrrolidin-1-yl, or 4-C_{1-4} alkylpiperazin-1-yl.

For certain embodiments, a hydrogen atom in the amino group at the 4-position (and/or in an amino group at another position) can be replaced with a group such as R_a'''-carbonyl, R_a'''-O-carbonyl, $N(R_a'''')(R_a''')$-carbonyl where R_a''' and R_a'''' are each independently C_{1-10} alkyl, C_{3-7} cycloalkyl, benzyl, or R_a'''-carbonyl is a natural α-aminoacyl or natural α-aminoacyl-natural α-aminoacyl, $-C(OH)C(O)OY_2$ wherein Y_2 is H, C_{1-6} alkyl or benzyl, $-C(OY_4)Y_{0a}$ wherein Y_4 is C_{1-4} alkyl and Y_{0a} is C_{1-6} alkyl, carboxyC_{1-6} alkyl, aminoC_{1-4} alkyl or mono-N- or di-N,N-C_{1-6} alkylaminoalkyl, $-C(Y_5)Y_{1a}$ wherein Y_5 is H or methyl and Y_{1a} is mon-N- or di-N,N-C_{1-6} alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

Compounds (including intermediates) of the present invention may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example proton tautomers (prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. When compounds of the present invention have a hydrogen atom at the 2-position, proton migration between the 2- and 3-positions may occur.

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The present invention embraces both solvated and unsolvated forms.

For any of the compounds presented herein, each one of the following variables (e.g., R_A, R_B, R_{A1}, R_{B1}, R, R_1, R_2, m, n, p, G, Q, X, Y, Z, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

In certain embodiments (e.g., of Formula I), R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

In certain embodiments (e.g., of Formula II, XIV, XV, or XVI), R_{A1} and R_{B1} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$;

or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

In certain embodiments (e.g., of Formula I or Formula II, XIV, XV, or XVI), R_A and R_B or R_{A1} and R_{B1} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

In certain embodiments (e.g., of Formula I or Formula II, XIV, XV, or XVI), R_A and R_B or R_{A1} and R_{B1} form a fused aryl or heteroaryl ring.

In certain embodiments (e.g., of Formula I), R_A and R_B are taken together to form a fused aryl ring wherein the ring is a benzo ring which is unsubstituted or substituted by one, two, three, or four R' groups.

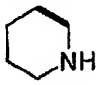
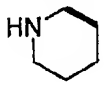
In certain embodiments (e.g., of Formula I or Formula II, XIV, XV, or XVI), R_A and R_B or R_{A1} and R_{B1} form a fused aryl ring. In certain embodiments, the fused aryl ring is benzo.

In certain embodiments (e.g., of Formula II, XIV, XV, or XVI), R_{A1} and R_{B1} are taken together to form a fused aryl ring, wherein the ring is a benzo ring which is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group.

In certain embodiments (e.g., of Formula I or Formula II), R_A and R_B or R_{A1} and R_{B1} form a fused heteroaryl ring. In certain embodiments, the fused heteroaryl ring is pyrido or thieno. In certain embodiments, the fused heteroaryl ring is pyrido. In certain of these embodiments, the pyrido ring is

 or  wherein the highlighted bond indicates the position where the ring is fused.

In certain embodiments (e.g., of Formula I or Formula II), R_A and R_B or R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring. In certain embodiments, the ring is a cyclohexene ring.

In certain embodiments (e.g., of Formula I or Formula II), R_A and R_B or R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S. In certain embodiments, the ring is tetrahydropyrido or dihydrothieno. In certain embodiments the heteroatom is N. In certain embodiments, the ring is tetrahydropyrido. In certain of these embodiments, the ring is  or  wherein the highlighted bond indicates the position where the ring is fused.

In certain embodiments (e.g., of Formula III), R_{A2} and R_{B2} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

In certain embodiments (e.g., of Formula III), R_{A2} and R_{B2} are independently hydrogen or alkyl.

In certain embodiments (e.g., of Formula III), R_{A2} and R_{B2} are both methyl.

In certain embodiments (e.g., of any one of Formulas X through XIII), R is selected from the group consisting of alkyl and haloalkyl.

In certain embodiments (e.g., including any one of the above embodiments of Formulas I, II, IV through IX, XIV, XV, and XVI where R is present), R is selected from the group consisting of alkyl, alkoxy, halogen, and hydroxy.

In certain embodiments (e.g., including any one of the above embodiments of Formulas I, II, IV through IX, XIV, XV, and XVI where R is present), R is hydroxy.

For certain embodiments (e.g., of Formulas IV or V), n is 0.

For certain embodiments (e.g., of Formula IV), n is 0 and m is 1.

For certain embodiments (e.g., of any one of Formulas VI through XIII), p is 0.

For certain embodiments (e.g., of any one of Formulas II, IV, VI through IX, XIV, XV, and XVI), including any one of the above embodiments which includes R_3, R_3 is selected from the group consisting of alkylsulfonylalkyleneoxy, alkylsulfonylaminoalkyleneoxy, alkylcarbonylaminoalkyleneoxy, aryl, arylalkyleneoxy, heteroaryl, heteroarylalkyleneoxy, heterocyclyl, heterocyclyloxy, heterocyclylalkyleneoxy, and heterocyclylcarbonylalkyleneoxy; wherein aryl and heteroaryl are unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, halogen, heterocyclylcarbonyl, and dialkylaminocarbonyl; and wherein heterocyclyl is unsubstituted or substituted by one or more substitutents selected from the group consisting of alkylsulfonyl, alkylcarbonyl, and oxo.

For certain embodiments (e.g., of any one of Formulas II, IV, VI through IX, XIV, XV, and XVI), including any one of the above embodiments which includes R_3, R_3 is selected from the group consisting of benzyloxy, (4-chlorobenzyl)oxy, (4-methylbenzyl)oxy, phenyl, *p*-tolyl, 2-ethoxyphenyl, 3-(morpholine-4-carbonyl)phenyl, 3-(*N,N*-dimethylaminocarbonyl)phenyl, 3-furyl, pyridin-3-yl, pyridin-4-yl, 6-chloropyridin-3-yl, 6-fluoropyridin-3-yl, 6-methylpyridin-3-yl, 5-(hydroxymethyl)pyridin-3-yl, and quinolin-3-yl.

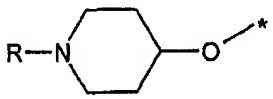
For certain embodiments (e.g., of any one of Formulas II, IV, VI through IX, XIV, XV, and XVI), including any one of the above embodiments which includes R_3, R_3 is selected from the group consisting of phenyl, *p*-tolyl, benzyloxy, (4-chlorobenzyl)oxy, (4-methylbenzyl)oxy, 3-furyl, pyridin-3-yl, 5-(hydroxymethyl)pyridin-3-yl, 6-chloropyridin-3-yl, 6-fluoropyridin-3-yl, 6-methylpyridin-3-yl, 3-quinolin-3-yl, and thiazol-4-ylmethoxy.

For certain embodiments (e.g., of any one of Formulas II, IV, VI through IX, XIV, XV, and XVI), including any one of the above embodiments which includes R_3, R_3 is pyridin-3-yl, pyridin-4-yl, 6-fluoropyridin-3-yl, 5-(hydroxymethyl)pyridin-3-yl, quinolin-3-yl, 2-ethoxyphenyl, or 3-(morpholine-4-carbonyl)phenyl.

For certain embodiments (e.g., of any one of Formulas II, IV, VI through IX, XIV, XV, and XVI), including any one of the above embodiments which includes R_3, R_3 is 2-oxo-1,3-oxazolidin-3-yl.

For certain embodiments (e.g., of any one of Formulas II, IV, VI through IX, XIV, XV, and XVI), including any one of the above embodiments which includes R_3, R_3 is 1,3-thiazol-4-ylmethoxy, (1-methyl-1*H*-imidazol-2-yl)methoxy, or pyridin-3-ylmethoxy.

For certain embodiments (e.g., of any one of Formulas II, IV, VI through IX, XIV, XV, and XVI), including any one of the above embodiments which includes R_3, R_3 is 2-pyrrolidin-1-ylethoxy, 2-(2-oxopyrrolidin-1-yl)ethoxy, 2-(1,1-dioxidoisothiazolidin-2-yl)ethoxy, 2-morpholin-4-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, 3-(1,1-dioxidoisothiazolidin-2-yl)propoxy, 3-morpholin-4-ylpropoxy, 2-morpholin-4-yl-2-oxoethoxy, and



, wherein R is alkylsulfonyl or alkylcarbonyl. For certain of these embodiments, alkyl is methyl, ethyl, or isopropyl.

For certain embodiments (e.g., of any one of Formulas II, IV, VI through IX, XIV, XV, and XVI), including any one of the above embodiments which includes R_3, R_3 is alkyl-$S(O)_2$-NH-$(CH_2)_{2-3}$-O-, alkyl-$S(O)_2$-$(CH_2)_{2-3}$-O-, or alkyl-C(O)-NH-$(CH_2)_{2-3}$-O-. For certain of these embodiments, alkyl is methyl, ethyl, or isopropyl.

For certain embodiments (e.g., of any one of Formulas II, IV, VI through IX, XIV, XV, and XVI), including any one of the above embodiments which includes R_3, R_3 is at the 7-position.

For certain embodiments (e.g., of any one of Formulas II, IV, VI through IX, XIV, XV, and XVI), including any one of the above embodiments which includes R_3, R_3 is at the 8-position.

For certain embodiments (e.g., of any one of Formulas IV, VI through IX), including any one of the above embodiments, m is 0.

For certain embodiments (e.g., of Formula IV), including any one of the above embodiments of Formula IV, n is 0, and m is 0.

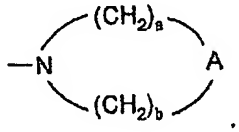
For certain embodiments (e.g., of any one of Formulas VI through IX), including any one of the above embodiments of Formulas VI through XI, p is 0, and m is 0.

For certain embodiments (e.g., of any one of Formulas I through XVI), including any one of the above embodiments, R_1 is R_4. For certain of these embodiments, R_4 is alkyl or arylalkylenyl. For certain of these embodiments, R_4 is methyl, ethyl, *n*-propyl, 1-methylethyl, *n*-butyl, 1-ethylpropyl, 2-methylpropyl, 3-methylbutyl, benzyl, 2-phenylethyl, or 3-phenylpropyl.

For certain embodiments (e.g., of any one of Formulas I through XVI), including any one of the above embodiments, R_1 is -X-N(R_8)-Y-R_4. For certain of these embodiments, X is C_{2-4} alkylene, R_8 is hydrogen, R_4 is C_{1-6} alkyl, Y is -C(O)-, -$S(O)_2$-, or -C(O)-N(R_{11})- wherein R_{11} is hydrogen or R_{11} and R_4 join to form a morpholine ring.

For certain embodiments, (e.g., of any one of Formulas XIV and XVI), including any one of the above embodiments of Formula XIV or XVI, X_1 is C_{1-4} alkylene, and A_1 is -N(R_8)-, or -N(-Y-R_4)-. For certain of these embodiments, A_1 is -N(R_8)-. For certain of these embodiments, R_8 is hydrogen, 2-hydroxyethyl, or benzyl. Alternatively, for certain of these embodiments, A_1 is -N(-Y-R_4)-.

For certain embodiments, (e.g., of any one of Formulas XIV and XVI), including any one of the above embodiments of Formula XIV or XVI where A_1 can be -N(-Y-R_4)-, X_1 is C_{1-4} alkylene, and Y is -C(O)-, -$S(O)_2$-, or -C(O)-N(R_{11})-. For certain of these embodiments, R_4 is C_{1-6} alkyl, and R_{11} is hydrogen or methyl. Alternatively, for certain of these embodiments, Y is -C(O)-N(R_{11})-, and R_4 and R_{11} form the group



. For certain of these embodiments, A is -CH_2- or -O-. For certain of these embodiments, a and b are each independently 1 or 2, with the proviso that when A is -O- then a and b are each 2.

For certain embodiments (e.g., of any one of Formulas I through XVI), including any one of the above embodiments, R_1' is hydrogen.

For certain embodiments (e.g., of any one of Formulas II through XVI), including any one of the above embodiments, R_2 is hydrogen, alkyl, alkoxyalkylenyl, or hydroxyalkylenyl.

For certain embodiments (e.g., of any one of Formulas II through XVI), including any one of the above embodiments, R_2 is C_{1-4} alkyl, C_{1-4} alkyl-O-C_{2-4} alkylenyl, or hydroxyC_{2-4} alkylenyl.

For certain embodiments (e.g., of any one of Formulas II through XVI), including any one of the above embodiments, R_2 is methyl, ethyl, *n*-propyl, *n*-butyl, 2-methoxyethyl, or 2-hydroxyethyl.

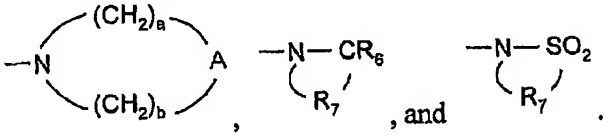
For certain embodiments, R_1 alkyl or arylalkylenyl.

For certain embodiments, R_1 is methyl, ethyl, *n*-propyl, 1-methylethyl, *n*-butyl, 1-ethylpropyl, 2-methylpropyl, 3-methylbutyl, benzyl, 2-phenylethyl, or 3-phenylpropyl.

For certain embodiments, R_1 is $-X-N(R_8)-Y-R_4$.

For certain embodiments, R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

or R_1 and R_1' together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



, , and .

For certain embodiments, R_1 is hydrogen.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, and R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded.

For certain embodiments, R_4 is aryl, heteroaryl, or heterocyclyl.

For certain embodiments, R_4 is alkyl, aryl, or heteroaryl.

For certain embodiments, R_4 is alkyl or arylalkylenyl.

For certain embodiments, R_4 is C_{1-6} alkyl.

For certain embodiments, R_4 is aryl.

For certain embodiments, R_4 is heteroaryl.

For certain embodiments, R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

For certain embodiments, R_4' is aryl, heteroaryl, or heterocyclyl.

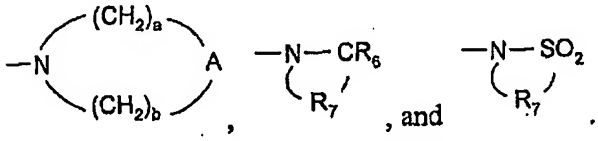
For certain embodiments, R_4' is alkyl, aryl, or heteroaryl.

For certain embodiments, R_4' is alkyl.

For certain embodiments, R_4' is aryl.

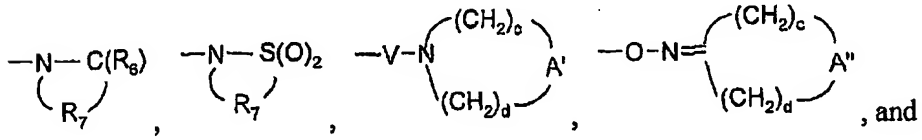
For certain embodiments, R_4' is heteroaryl.

For certain embodiments, R_5 is selected from the group consisting of:

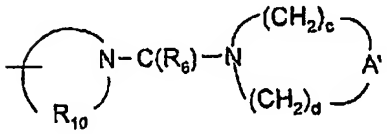


, and .

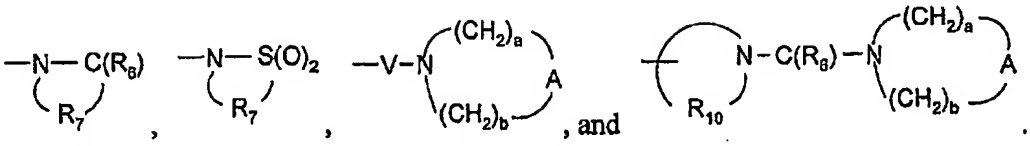
For certain embodiments, R_5' is selected from the group consisting of:



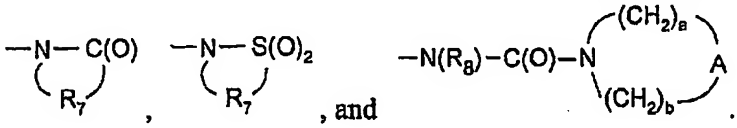
, and



For certain embodiments, R_5' is selected from the group consisting of



For certain embodiments, R_5' is selected from the group consisting of



For certain embodiments, R_6 is selected from the group consisting of =O and =S.

For certain embodiments, R_6 is =O.

For certain embodiments, R_6 is =S.

For certain embodiments, R_7 is C_{2-7} alkylene.

For certain embodiments, R_7 is C_{3-4} alkylene.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl.

For certain embodiments, R_8 is hydrogen.

For certain embodiments, R_8 is alkyl.

For certain embodiments, R_8 is hydrogen, 2-hydroxyethyl, or benzyl.

For certain embodiments, R_8 is 2-hydroxyethyl.

For certain embodiments, R_8 is benzyl.

For certain embodiments, R_9 is selected from the group consisting of hydrogen and alkyl.

For certain embodiments, R_9 is alkyl.

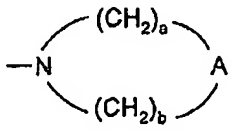
For certain embodiments, R_9 is hydrogen.

For certain embodiments, R_{10} is C_{3-8} alkylene.

For certain embodiments, R_{10} is C_{4-5} alkylene.

For certain embodiments, R_{11} is hydrogen or methyl.

For certain embodiments, R_{11} is hydrogen.

For certain embodiments, R_4 and R_{11} form the group  wherein A is $-CH_2-$ or -O-, and a and b are each independently 1 or 2, with the proviso that when A is -O- then a and b are each 2.

For certain of these embodiments, R_{11} and R_4 join to form a morpholine ring.

For certain of these embodiments, R_{11} and R_4 join to form a 4 to 6 membered ring.

For certain of these embodiments, R_{11} and R_4 join to form a pyrrolidine ring.

For certain of these embodiments, R_{11} and R_4 join to form a piperidine ring.

For certain embodiments, A is selected from the group consisting of -CH(R_8)-, -O-, -N(R_8)-, -N(Y-R_4)-, and -N(X-N(R_8)-Y-R_4)-.

For certain embodiments, A is selected from the group consisting of -CH(R_8)-, -O-, and -N(R_8)-.

For certain embodiments, A is $-CH_2-$ or -O-.

For certain embodiments, A is -O-.

For certain embodiments, A_1 is selected from the group consisting of -N(R_8)- and -N(-Y-R_4)-.

For certain embodiments, A_1 is -N(R_8)-.

For certain embodiments, A_1 is -N(-Y-R_4)-.

For certain embodiments, A' is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and -N(R_4)-.

For certain embodiments, A' is -O-.

For certain embodiments, A" is selected from the group consisting of -O-, $-S(O)_{0-2}-$, -N(-Q-R_4)-, and $-CH_2-$.

For certain embodiments, including any one of the above embodiments of Formula XV or XVI, G is selected from the group consisting of -C(O)-R'", α-aminoacyl, and -C(O)-O-R'". For certain of these embodiments, R'" contains one to ten carbon atoms. For certain of these embodiments, α-aminoacyl is an α-C_{2-11} aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids containing a total of at least 2 carbon atoms and a total of up to 11 carbon atoms, and may also include one or more heteroatoms selected from the group consisting of O, S, and N.

For certain embodiments, including any one of the above embodiments which include an α-aminoacyl group, α-aminoacyl is an α-aminoacyl group derived from a naturally occuring α-amino acid selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, including any one of the above embodiments which include an α-aminoacyl group, α-aminoacyl is an α-aminoacyl group derived from an α-

amino acid found in proteins, wherein the the amino acid is selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$.

For certain embodiments, Q is a bond, $-C(R_6)-$, $-S(O)_2-$, or $-C(R_6)-N(R_8)-W-$.

For certain embodiments, Q is a bond.

For certain embodiments, V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$.

For certain embodiments, V is $-C(R_6)-$.

For certain embodiments, V is $-N(R_8)-C(R_6)-$.

For certain embodiments, W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$.

For certain embodiments, W is selected from the group consisting of a bond and $-C(O)-$.

For certain embodiments, W is a bond.

For certain embodiments, X is C_{2-20} alkylene.

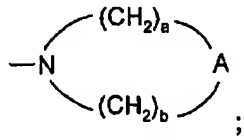
For certain embodiments, X is C_{2-4} alkylene.

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups.

For certain embodiments, X' is C_{1-4} alkylene.

For certain embodiments, X_1 is C_{1-4} alkylene.

For certain embodiments, X_1 is methylene or ethylene.

For certain embodiments, Y is selected from the group consisting of $-C(R_6)-$, $-C(R_6)-O-$, $-S(O)_2-$, $-S(O)_2-N(R_8)-$, and $-C(R_6)-N(R_{11})-$; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group 

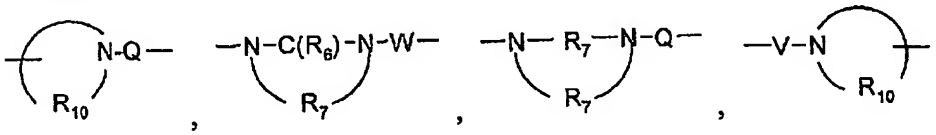
;

a and b are independently integers from 1 to 4 with the proviso that when A is

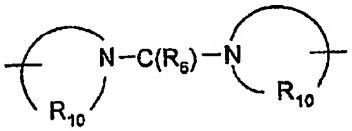
-O-, -N(R_8)-, -N(Y-R_4)-, or -N(X-N(R_8)-Y-R_4)- then a and b are independently integers from 2 to 4.

For certain embodiments, Y is -C(O)-, -S(O)$_2$-, or -C(O)-N(R_{11})-. For certain of these embodiments, R_{11} is hydrogen. For certain of these embodiments, R_{11} and R_4 join to form a morpholine ring.

For certain embodiments, Y' is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-, -O-N(R_8)-Q-, -O-N=C(R_6)-, -C(=N-O-R_8)-, -CH(-N(-O-R_8)-Q-R_4)-,



, and



For certain embodiments, Y' is -C(O)-, -S(O)$_2$-, -NH-S(O)$_2$-, or -NH-C(O)-.

For certain embodiments, Y' is -S(O)$_2$-, -NH-S(O)$_2$-, or -NH-C(O)-.

For certain embodiments, Z is a bond or -O-.

For certain embodiments, a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -N(R_8)-, -N(Y-R_4)-, or -N(X-N(R_8)-Y-R_4)- then a and b are independently integers from 2 to 4.

For certain embodiments, a and b are each independently 1 or 2, with the proviso that when A is -O- then a and b are each 2.

For certain embodiments, c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7. For certain embodiments, c and d are each the integer 2.

For certain embodiments, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, or any one of the above embodiments in combination with a pharmaceutically acceptable carrier.

For certain embodiments, the present invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII,

XIII, XIV, XV, XVI, or any one of the above embodiments or administering any one of the above pharmaceutical compositions to the animal. For certain of these embodiments, the cytokine is selected from the group consisting of IFN-α, TNF-α, IL-6, IL-10, and IL-12. For certain of these embodiments, the cytokine is IFN-α or TNF-α.

For certain embodiments, the present invention provides a method of treating a viral disease in an animal comprising administering a therapeutically effective amount of a compound or salt of any one of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, or any one of the above embodiments or administering any one of the above pharmaceutical compositions to the animal.

For certain embodiments, the present invention provides a method of treating a neoplastic disease in an animal comprising administering a therapeutically effective amount of a compound or salt of any one of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, or any one of the above embodiments or administering any one of the above pharmaceutical compositions to the animal.

Preparation of the Compounds

Compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wisconsin, USA) or are readily prepared using methods well known to those skilled in the art (e.g. prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, New York, (1967-1999 ed.); Alan R. Katritsky, Otto Meth-Cohn, Charles W. Rees, *Comprehensive Organic Functional Group Transformations*, v 1-6, Pergamon Press, Oxford, England, (1995); Barry M. Trost and Ian Fleming, *Comprehensive Organic Synthesis*, v. 1-8, Pergamon Press, Oxford, England, (1991); or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. Ed. Springer-Verlag, Berlin, Germany, including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For more detailed description of the individual reaction steps, see the EXAMPLES section below. Those skilled in the art will appreciate that other synthetic

routes may be used to synthesize the compounds of the invention. Although specific starting materials and reagents are depicted in the reaction schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional methods well known to those skilled in the art.

In the preparation of compounds of the invention it may sometimes be necessary to protect a particular functionality while reacting other functional groups on an intermediate. The need for such protection will vary depending on the nature of the particular functional group and the conditions of the reaction step. Suitable amino protecting groups include acetyl, trifluoroacetyl, *tert*-butxoycarbonyl (Boc), benzyloxycarbonyl, and 9-fluorenylmethyleneoxycarbonyl. Suitable hydroxy protecting groups include acetyl and silyl groups such as the *tert*-butyl dimethylsilyl group. For a general description of protecting groups and their use, see T. W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, USA, 1991.

Conventional methods and techniques of separation and purification can be used to isolate compounds of the invention, as well as various intermediates related thereto. Such techniques may include, for example, all types of chromatography (high performance liquid chromatography (HPLC), column chromatography using common absorbents such as silica gel, and thin layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

In some embodiments, compounds of the invention can be prepared according to Reaction Scheme I where R, R_1, R_2, and n are as defined above.

In step (1) of Reaction Scheme I, a 2-aminophenylacetonitrile of Formula XX is reacted with acetonylacetone to provide a substituted 2,5-dimethylpyrrole of Formula XXI. The reaction can be carried out by combining a 2-aminophenylacetonitrile of Formula XX with acetonylacetone along with a catalytic amount of *p*-toluenesulfonic acid in a suitable solvent such as toluene. The reaction can be heated at an elevated temperature such as at the reflux temperature.

In step (2) of Reaction Scheme I, a substituted 2,5-dimethylpyrrole of Formula XXI is acylated to provide an oxalated compound of Formula XXII. The acylation can be

carried out by adding a compound of Formula XXI and diethyl oxalate to a solution of sodium *tert*-butoxide in a suitable solvent such as ethanol and then heating at reflux under an inert atmosphere.

In step (3) of Reaction Scheme I, an oxalated compound of Formula XXII is reacted with a hydrazine of the Formula R_2NHNH_2 to provide a pyrazolo[3,4-*c*]quinolin-1-amine of Formula XXIII. The reaction can be carried out by adding a solution of the hydrazine in acetic acid to a solution of a compound of Formula XXII in a suitable solvent such as ethanol. The reaction can be carried out at an elevated temperature such as the reflux temperature of the solvent.

In step (4) of Reaction Scheme I, a pyrazolo[3,4-*c*]quinolin-1-amine of Formula XXIII is chlorinated to provide a 4-chloropyrazolo[3,4-*c*]quinolin-1-amine of Formula XXIV. The reaction can be carried out by combining a compound of Formula XXIII with phosphorus oxychloride and heating.

In step (5a) of Reaction Scheme I, 4-chloropyrazolo[3,4-*c*]quinolin-1-amine of Formula XXIV or a salt thereof is treated with a ketone, aldehyde, or corresponding ketal or acetal thereof, under acidic conditions to provide a 4-chloropyrazolo[3,4-*c*]quinolin-1-imine of Formula XXV. For example, a ketone is added to a solution of the hydrochloride salt of a compound of Formula XXIV in a suitable solvent such as isopropanol in the presence of an acid or acid resin, for example, DOWEX W50-X1 acid resin. The ketone, aldehyde, or corresponding ketal or acetal, is selected with R_i and R_{ii} groups that will provide the desired R_1 substituent. For example, acetone will provide a compound where R_1 is isopropyl, and benzaldehyde will provide a compound where R_1 is benzyl. The reaction is run with sufficient heating to drive off the water formed as a byproduct of the reaction.

In step (6) of Reaction Scheme I, a 4-chloropyrazolo[3,4-*c*]quinolin-1-imine of Formula XXV is reduced to provide a 4-chloropyrazolo[3,4-*c*]quinolin-1-amine of Formula XXVI. The reaction can be carried out by adding sodium borohydride to a solution of a compound of Formula XXV in a suitable solvent such as methanol at ambient temperature.

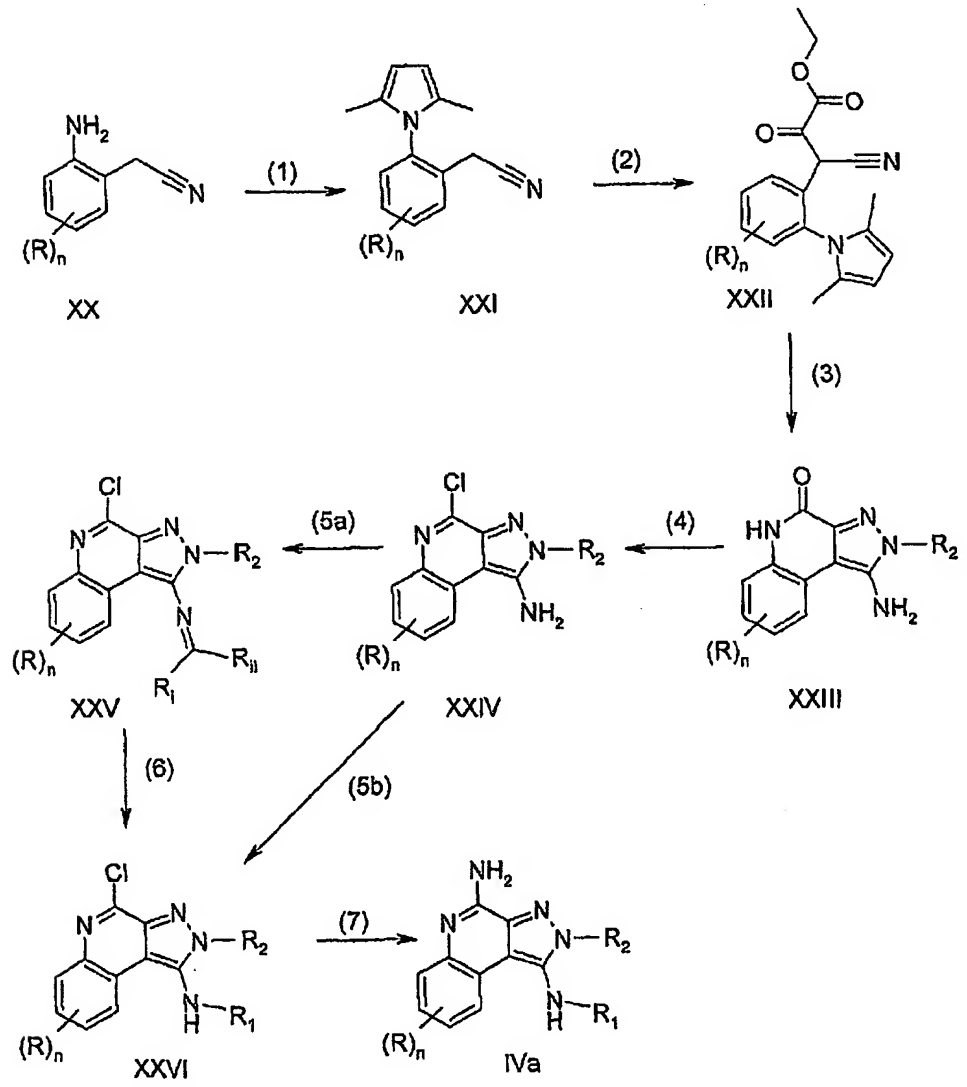
Alternatively, in step (5b) of Reaction Scheme I, a 4-chloropyrazolo[3,4-*c*]quinolin-1-amine of Formula XXIV can be treated with a ketone and a borohydride under acidic conditions to provide a 4-chloropyrazolo[3,4-*c*]quinolin-1-amine of Formula

XXVI. The reaction can be carried out at ambient temperature in a suitable solvent such as 1,2-dichloroethane.

Steps (5) and (6) are omitted for compounds where R_1 is hydrogen.

In step (7) of Reaction Scheme I, the chloro group of a pyrazolo[3,4-*c*]quinolin-1-amine of Formula XXVI is displaced to provide a pyrazolo[3,4-*c*]quinolin-1,4-diamine of Formula IVa, which is a subgenus of Formulas I, II, and IV. The reaction can be carried out by combining a compound of Formula XXVI with a solution of ammonia in methanol and heating the mixture in a sealed reactor.

Reaction Scheme I



In some embodiments, compounds of the invention can be prepared according to Reaction Scheme II where R_1, R_1', R_2, and n are as defined above and R_a is a subset of R that does not include halogen or alkenyl.

In step (1) of Reaction Scheme II, an indole of Formula XXVII is acylated to provide an oxalated indole of Formula XXVIII. The reaction can be carried out by adding ethyl chlorooxoacetate to a solution of an indole of Formula XXVII in a suitable solvent such as diethyl ether in the presence of pyridine. The reaction can be carried out at a sub-ambient temperature such as 0 °C. Many indoles of Formula XXVII are known. Some are commercially available and others can be readily prepared using known synthetic methods.

In step (2) of Reaction Scheme II, an oxalated indole of Formula XXVIII is rearranged to a pyrazolo[3,4-*c*]quinolin-4-one of Formula XXIX. The reaction can be carried out by adding a hydrazine of Formula R_2NHNH_2 to a solution of an oxalated indole of Formula XXVIII in a solvent or solvent mix such as ethanol/acetic acid in the presence of hydrochloric acid. The reaction can be carried out at an elevated temperature such as at reflux.

If step (2) is carried out using hydrazine, the resulting pyrazolo[3,4-*c*]quinolin-4-one of Formula XXIX where R_2 is hydrogen can be further elaborated using known synthetic methods. For example, a pyrazolo[3,4-*c*]quinolin-4-one of Formula XXIX where R_2 is hydrogen can be alkylated. The alkylation can be carried out by treating a solution of a pyrazolo[3,4-*c*]quinolin-4-one of Formula XXIX, where R_2 is hydrogen, with a base such as sodium ethoxide followed by the addition of an alkyl halide. The reaction can be run in a suitable solvent such as ethanol and can be carried out at an elevated temperature, for example, the reflux temperature of the solvent, or at ambient temperature. Alternatively, a pyrazolo[3,4-*c*]quinolin-4-one of Formula XXIX where R_2 is hydrogen can undergo a Buchwald amination with an aryl halide or heteroaryl halide. Numerous alkyl halides, aryl halides, and heteroaryl halides are commercially available; others can be prepared using known synthetic methods.

Step (2) can also be carried out using a hydrazine that will install a removable group at R_2. Examples of such hydrazines include benzylhydrazine and *tert*-butylhydrazine. At a later point in the synthetic pathway the group can be removed using

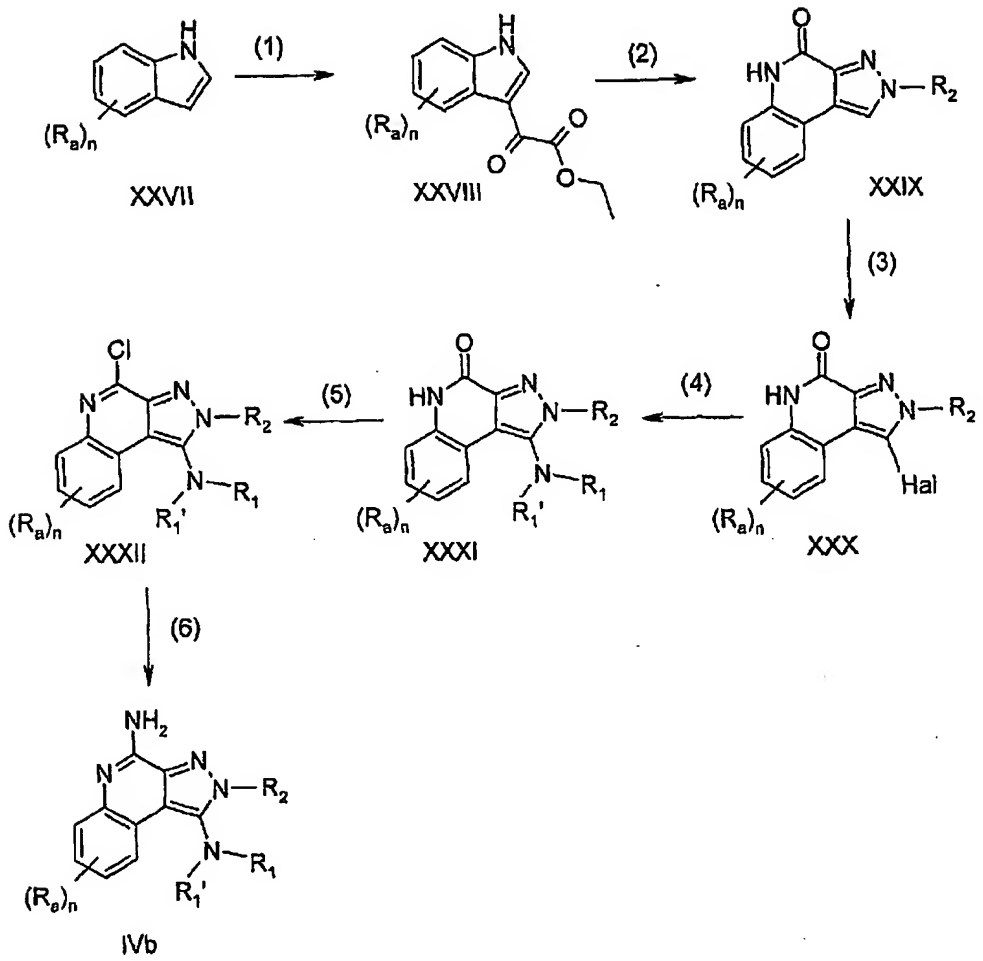
conventional methods to provide a compound in which R_2 is hydrogen. The compound may then be further elaborated using the methods described above.

In step (3) of Reaction Scheme II, a pyrazolo[3,4-*c*]quinolin-4-one of Formula XXIX is halogenated using conventional methods. The reaction can be carried out by deprotonating a compound of Formula XXIX with *n*-butyl lithium and then adding iodine.

In step (4) of Reaction Scheme II, the halogen group on a pyrazolo[3,4-*c*]quinolin-4-one of Formula XXX is displaced with an amine of Formula $HN(R_1)(R_1')$. Either thermal or catalytic, using palladium for example, displacement methods can be used.

Steps (5) and (6) can be carried out using the methods of steps (4) and (7) respectively of Reaction Scheme I to provide a provide a pyrazolo[3,4-*c*]quinolin-1,4-diamine of Formula IVb, which is a subgenus of Formulas I, II, and IV.

Reaction Scheme II



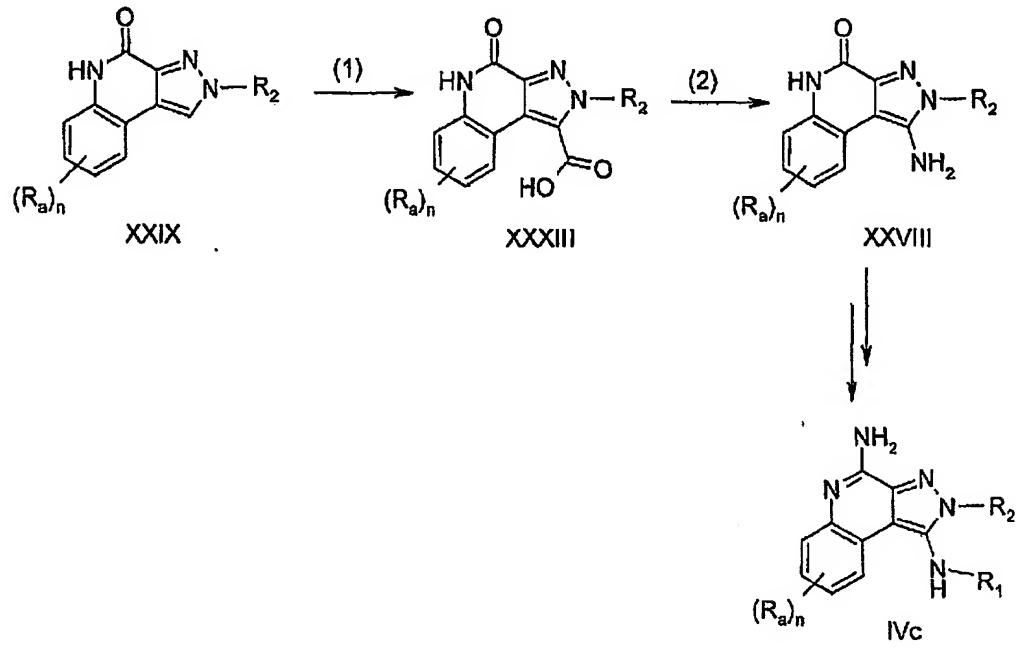
In some embodiments, compounds of the invention can be prepared according to Reaction Scheme III where R_a, R_1, R_2, and n are as defined above.

In step (1) of Reaction Scheme III, a carboxyl group is installed on a pyrazolo[3,4-*c*]quinolin-4-one of Formula XXIX. The reaction can be carried out by deprotonating a compound of Formula XXIX with *n*-butyl lithium and then quenching with carbon dioxide.

In step (2) of Reaction Scheme III, a pyrazolo[3,4-*c*]quinolin-4-one of Formula XXXIII is treated with diphenyl phosphoryl azide to provide a pyrazolo[3,4-*c*]quinolin-1-amine of Formula XXIII.

The remaining steps can be carried out using the methods of steps (4) through (7) of Reaction Scheme I to provide a pyrazolo[3,4-*c*]quinolin-1,4-diamine of Formula IVc.

Reaction Scheme III



For some embodiments, compounds of the invention can be prepared according to Reaction Scheme IV, wherein R_1, R_1', and R_2 are defined as above and R_{3b} and R_{3c} are defined below, and R_{4a} is methyl or benzyl.

Steps (1) through (6) of Reaction Scheme IV can be carried out as described for steps (1) through (6) of Reaction Scheme II. Some benzyloxy-substituted indoles and methoxy-substituted indoles of Formula XXXIV are known; others can be prepared using known synthetic methods.

In step (7) of Reaction Scheme IV, the benzyl or methyl group of pyrazolo[3,4-*c*]quinoline of Formula IVd, which is a subgenus of Formula IV, is cleaved using conventional methods to provide pyrazolo[3,4-*c*]quinolinol of Formula IVe, which is a subgenus of Formula IV. Cleavage of the benzyl group can be carried out on a Parr apparatus under hydrogenolysis conditions using a suitable heterogeneous catalyst such as palladium on carbon in a solvent such as ethanol. Alternatively, the reaction can be

carried out by transfer hydrogenation in the presence of a suitable hydrogenation catalyst. The transfer hydrogenation can be carried out by adding ammonium formate to a solution of a pyrazolo[3,4-*c*]quinoline of Formula IVd in a suitable solvent such as ethanol in the presence of a catalyst such as palladium on carbon. The reaction can be carried out at an elevated temperature, for example, the reflux temperature of the solvent. Demethylation can be carried out by treating a pyrazolo[3,4-*c*]quinoline of Formula IVd with a solution of boron tribromide in a suitable solvent such as dichloromethane. The reaction can be carried out at a sub-ambient temperature such as 0 °C. Alternatively, the demethylation can be carried out by heating a pyrazolo[3,4-*c*]quinoline of Formula IVd with anhydrous pyridinium chloride at an elevated temperature, such as 210 °C.

In step (8a) of Reaction Scheme IV, the hydroxy group of a pyrazolo[3,4-*c*]quinolinol of Formula IVe is activated by conversion to a trifluromethanesulfonate (triflate) group. The reaction can be carried out by treating a pyrazolo[3,4-*c*]quinolinol of Formula IVe with *N*-phenyl-bis(trifluoromethanesulfonamide) in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature in a suitable solvent such as DMF.

Step (9) of Reaction Scheme IV can be carried out using known palladium-catalyzed coupling reactions such as the Suzuki coupling, Heck reaction, the Stille coupling, and the Sonogashira coupling. For example, a triflate-substituted pyrazolo[3,4-*c*]quinoline of Formula XXXV undergoes Suzuki coupling with a boronic acid of Formula R_{3b}-B(OH)$_2$, an anhydride thereof, or a boronic acid ester of Formula R_{3b}-B(O-alkyl)$_2$; wherein R_{3b} is -R_{4b}, -X_e-R_4, -X_f-Y-R_4, or -X_f-R_5; where X_e is alkenylene; X_f is arylene, heteroarylene, and alkenylene interrupted or terminated by arylene or heteroarylene; R_{4b} is aryl or heteroaryl where the aryl or heteroaryl groups can be unsubstituted or substituted as defined in R_4 above; and R_4, R_5, and Y are as defined above. The coupling can be carried out by combining a triflate-substituted pyrazolo[3,4-*c*]quinoline of Formula XXXV with a boronic acid or an ester or anhydride thereof in the presence of palladium (II) acetate, triphenylphosphine, and a base such as aqueous sodium carbonate in a suitable solvent such as *n*-propanol. The reaction can be carried out at an elevated temperature, for example, at the reflux temperature. Numerous boronic acids of Formula R_{3b}-B(OH)$_2$, anhydrides thereof, and boronic acid esters of Formula R_{3b}-B(O-alkyl)$_2$ are commercially available; others can be readily prepared using known synthetic methods.

Alternatively, the Heck reaction can be used in step (9) of Reaction Scheme IV to provide compounds of Formula IVg, wherein R_{3b} is $-X_e-R_{4b}$ or $-X_e-Y-R_4$, wherein X_e, Y, R_4, and R_{4b} are as defined above. The Heck reaction can be carried out by coupling a triflate-substituted pyrazolo[3,4-*c*]quinoline of Formula XXXV with a compound of the Formula $H_2C=C(H)-R_{4b}$ or $H_2C=C(H)-Y-R_4$. Several of these vinyl-substituted compounds are commercially available; others can be prepared by known methods. The reaction can be carried out by combining a triflate-substituted pyrazolo[3,4-*c*]quinoline of Formula XXXV and the vinyl-substituted compound in the presence of palladium (II) acetate, triphenylphosphine or tri-*ortho*-tolylphosphine, and a base such as triethylamine in a suitable solvent such as acetonitrile or toluene. The reaction can be carried out at an elevated temperature such as 100-120 °C under an inert atmosphere.

Compounds of Formula IVg, wherein R_{3b} is $-X_g-R_4$, X_g is alkynylene, and R_4 is as defined above, can also be prepared by palladium catalyzed coupling reactions such as the Stille coupling or Sonogashira coupling. These reactions are carried out by coupling a triflate-substituted pyrazolo[3,4-*c*]quinoline of Formula XXXV with a compound of the Formula $(alkyl)_3Sn-C\equiv C-R_4$, $(alkyl)_3Si-C\equiv C-R_4$, or $H-C\equiv C-R_4$.

Compounds of Formula IVg prepared as described above by palladium-mediated coupling reactions, wherein R_{3b} is $-X_e-R_4$, $-X_e-Y-R_4$, $-X_{f2}-Y-R_4$, $-X_{f2}-R_5$, or $-X_g-R_4$, where X_{f2} is alkenylene interrupted or terminated by arylene or heteroarylene, and X_e, X_g, Y, R_4, and R_5 are as defined above, can undergo reduction of the alkenylene or alkynylene group present to provide pyrazolo[3,4-*c*]quinolines of Formula IVg wherein R_{3b} is $-X_h-R_4$, $-X_h-Y-R_4$, $-X_i-Y-R_4$, or $-X_i-R_5$, where X_h is alkylene; X_i is alkylene interrupted or terminated by arylene or heteroarylene; and R_4, R_5, and Y are as defined above. The reduction can be carried out by hydrogenation using a conventional heterogeneous hydrogenation catalyst such as palladium on carbon. The reaction can be carried out on a Parr apparatus in a suitable solvent such as ethanol, methanol, or mixtures thereof.

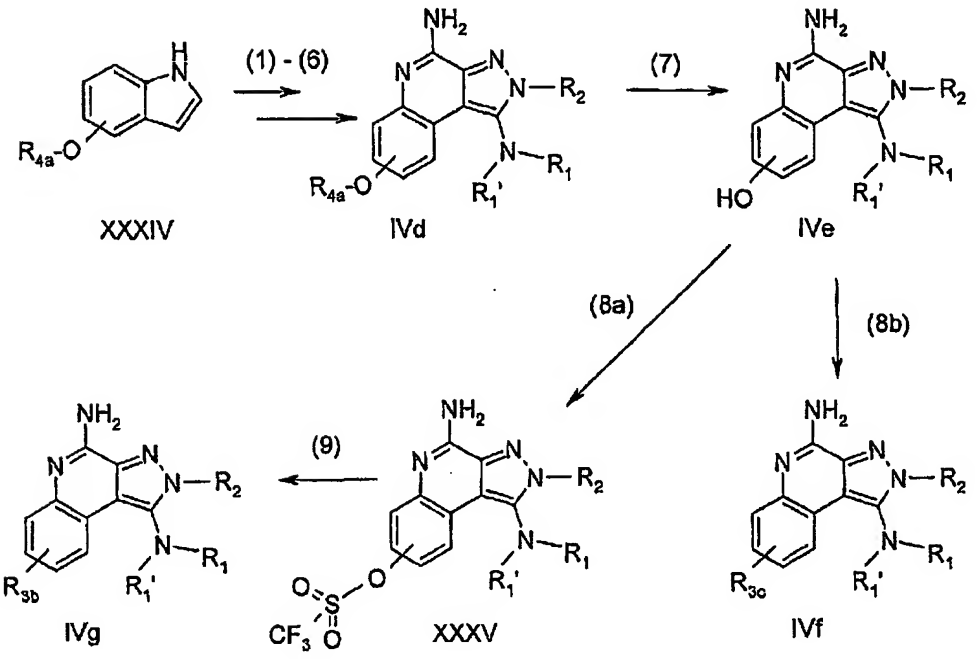
In step (8b) of Reaction Scheme IV, a pyrazolo[3,4-*c*]quinolinol of Formula IVe is converted to a pyrazolo[3,4-*c*]quinoline of Formula IVf, wherein R_{3c} is $-O-R_4$, $-O-X-R_4$, $-O-X-Y-R_4$, or $-O-X-R_5$, and X, Y, R_4, and R_5 are as defined above, using a Williamson-type ether synthesis. The reaction can be effected by treating a pyrazolo[3,4-*c*]quinolinol of Formula IVe with an aryl, alkyl, or arylalkylenyl halide of Formula Halide-R_4, Halide-alkylene-R_4, Halide-alkylene-Y-R_4, or Halide-alkylene-R_5 in the presence of a base.

Numerous alkyl, arylalkylenyl, and aryl halides of these formulas are commercially available, including substituted benzyl bromides and chlorides, substituted or unsubstituted alkyl or arylalkylenyl bromides and chlorides, bromo-substituted ketones, esters, and heterocycles, and substituted fluorobenzenes. Other halides of these formulas can be prepared using conventional synthetic methods. The reaction can be carried out by combining an alkyl, arylalkylenyl, or aryl halide with a pyrazolo[3,4-*c*]quinolinol of Formula IVe in a solvent such as DMF or *N,N*-dimethylacetamide in the presence of a suitable base such as cesium carbonate. Optionally, catalytic tetrabutylammonium bromide can be added. The reaction can be carried out at ambient temperature or at an elevated temperature, for example 50 °C or 85 °C, depending on the reactivity of the halide reagent.

Alternatively, step (8b) may be carried out using the Ullmann ether synthesis, in which an alkali metal aryloxide prepared from a pyrazolo[3,4-*c*]quinolinol of Formula IVe reacts with an aryl halide in the presence of copper salts, to provide a pyrazolo[3,4-*c*]quinoline of Formula IVe, where R_{3c} is -O-R_{4b}, -O-X_j-R_4, or -O-X_j-Y-R_4, wherein X_j is an arylene or heteroarylene and R_{4b} is as defined above. Numerous substituted and unsubstituted aryl halides are commercially available; others can be prepared using conventional methods.

The methods described in steps (7) through (9) and (7) through (8b) can also be used to install R_{3b} or R_{3c} groups at an earlier stage in the synthetic pathway.

Reaction Scheme IV

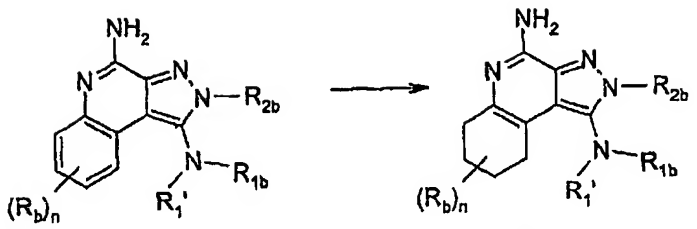


For some embodiments, compounds of the invention can be prepared according to Reaction Scheme V, where R_b, R_{1b}, and R_{2b} are subsets of R, R_1, and R_2 as defined above that do not include those substituents which would be susceptible to reduction under the acidic hydrogenation conditions of the reaction and n is as defined above.

In Reaction Scheme V, a pyrazolo[3,4-*c*]quinoline of Formula IVh is reduced to provide a 6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinoline of Formula Va, which is a subgenus of Formulas I, II, and V. The reaction may be carried out under heterogeneous hydrogenation conditions by adding platinum (IV) oxide to a solution or suspension of a pyrazolo[3,4-*c*]quinoline of Formula IVh in a suitable solvent such as trifluoroacetic acid and placing the reaction under hydrogen pressure.

Alternatively, the reduction may be carried out at an earlier stage in the synthetic pathway.

Reaction Scheme V



Pyrazolo[3,4-*c*]naphthyridines of the invention can be prepared by using an azaindole as the starting material in Reaction Schemes II and IV. Azaindoles are known compounds. Some are commercially available and others can be prepared using known synthetic methods. Alternatively, pyrazolo[3,4-*c*]naphthyridines of the invention can be prepared by using a 2-aminopyridinylaceotonitrile as the starting material in Reaction Scheme I.

6,7,8,9-Tetrahydro-2*H*-pyrazolo[3,4-*c*]naphthyridines can be prepared by reducing pyrazolo[3,4-*c*]naphthyridines using the method of Reaction Scheme V.

For some embodiments, compounds of the invention can be prepared according to Reaction Scheme VI where R_a, R_1, R_2, and n are as defined above.

In step (1) of Reaction Scheme VI, a pyrazolo[3,4-*c*]quinolin-4-one of Formula XXXIII is chlorinated to provide a 4-chloropyrazolo[3,4-*c*]quinoline-1-carbonyl chloride of Formula XXXVI. The reaction can be carried out by combining a compound of Formula XXXIII with an excess of thionyl chloride in a suitable solvent such as toluene and heating at an elevated temperature such as, for example, the reflux temperature of the solvent.

In step (2) of Reaction Scheme VI, a 4-chloropyrazolo[3,4-*c*]quinoline-1-carbonyl chloride of Formula XXXVI is reacted with sodium azide to provide a 4-chloropyrazolo[3,4-*c*]quinoline-1-carbonyl azide of Formula XXXVII. The reaction can be carried out by treating a solution of a compound of Formula XXXVI in a suitable solvent such as acetone with a solution of sodium azide in water. The reaction can be carried out at a sub-ambient temperature such as, for example, 0 °C.

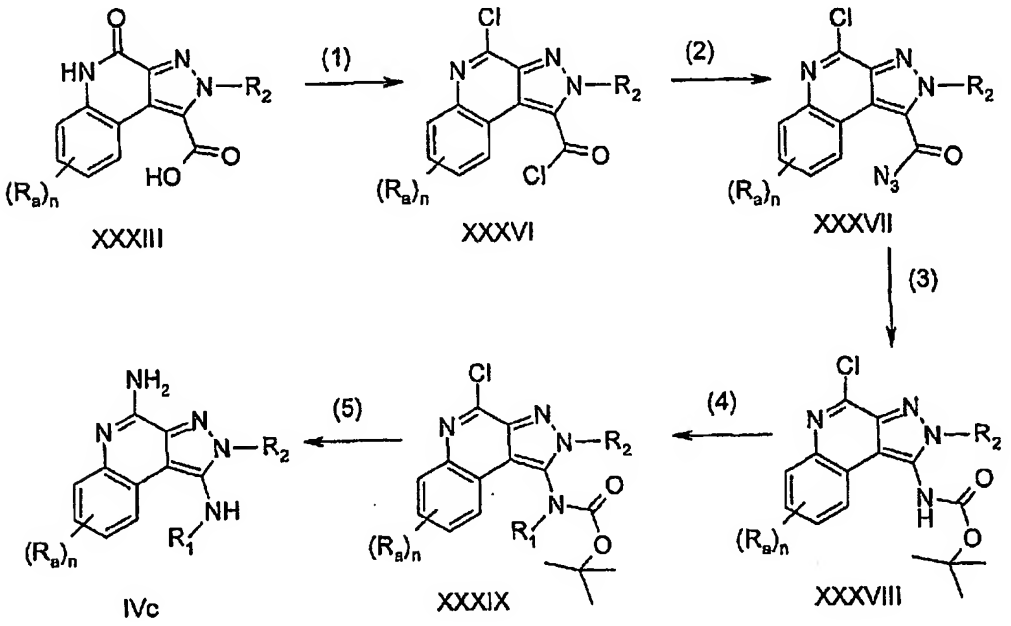
In step (3) of Reaction Scheme VI, a 4-chloropyrazolo[3,4-*c*]quinoline-1-carbonyl azide of Formula XXXVII undergoes a Curtius rearrangement in the presence of *tert*-

butanol to provide a *tert*-butyl 4-chloropyrazolo[3,4-*c*]quinolin-1-ylcarbamate of Formula XXXVIII. The reaction can be carried out by combing a compound of Formula XXXVII with an excess of *tert*-butanol in a suitable solvent such as toluene and heating at an elevated temperature such as, for example, the reflux temperature of the solvent.

In step (4) of Reaction Scheme VI, a *tert*-butyl 4-chloropyrazolo[3,4-*c*]quinolin-1-ylcarbamate of Formula XXXVIII is reacted with an iodide of Formula I-R_1 to provide a *tert*-butyl 4-chloropyrazolo[3,4-*c*]quinolin-1-ylcarbamate of Formula XXXIX. The reaction can be carried out by treating a solution of a compound of XXXVIII and an iodide of Formula I-R_1 in a suitable solvent such as tetrahydrofuran with sodium hydride. The reaction can be carried out at ambient temperature.

In step (5) of Reaction Scheme VI, the chloro group of a *tert*-butyl 4-chloropyrazolo[3,4-*c*]quinolin-1-ylcarbamate of Formula XXXIX is displaced and the Boc group is removed to provide a pyrazolo[3,4-*c*]quinolin-4-amine of Formula IVc. The reaction can be carried out by combining a compound of Formula XXXIX with a solution of ammonia in methanol in a pressure vessel and heating at an elevated temperature such as 150 °C.

Reaction Scheme VI



For some embodiments, compounds of the invention can be prepared according to Reaction Scheme VII where R_a, R_1, R_2, R_4, R_8, Y, and n are as defined above, Boc is *tert*-butoxycarbonyl, and X_{1a} is C_{1-4}alkylene.

In step (1) of Reaction Scheme VII, a *tert*-butyl 4-chloropyrazolo[3,4-*c*]quinolin-1-ylcarbamate of Formula XXXVIII is reacted with a Boc protected 4-(iodoalkyl)piperidine of Formula XL to provide a *tert*-butyl 4-chloropyrazolo[3,4-*c*]quinolin-1-ylcarbamate of Formula XLI. The reaction can be carried out as described in step (4) of Reaction Scheme VI.

In step (2) of Reaction Scheme VII, the chloro group of a *tert*-butyl 4-chloropyrazolo[3,4-*c*]quinolin-1-ylcarbamate of Formula XLI is displaced and one of the Boc groups is removed to provide a pyrazolo[3,4-*c*]quinolin-4-amine of Formula XIVa. The reaction can be carried out as described in step (5) of Reaction Scheme VI.

In step (3) of Reaction Scheme VII, the Boc group is removed from a pyrazolo[3,4-*c*]quinolin-4-amine of Formula XIVa to provide a pyrazolo[3,4-*c*]quinolin-4-amine of Formula XIVb. The reaction can be carried out by treating a solution or suspension of a compound of Formula XIVa in a suitable solvent such as ethanol with a strong acid such as hydrochloric acid. The reaction can be run at an elevated temperature such as, for example, the reflux temperature of the solvent.

In step (4a) of Reaction Scheme VII, the piperidinyl group in a pyrazolo[3,4-*c*]quinolin-4-amine of Formula XIVb is further elaborated using conventional methods to provide pyrazolo[3,4-*c*]quinolin-4-amine of Formula XIVc. For example, a compound of Formula XIVb or a salt thereof can react with an acid chloride of Formula $R_4C(O)Cl$ to provide a compound of Formula XIVc in which Y is -C(O)-. In addition, a compound of Formula XIVb can react with a sulfonyl chloride of Formula $R_4S(O)_2Cl$ or a sulfonic anhydride of Formula $(R_4S(O)_2)_2O$ to provide a compound of Formula XIVc in which Y is $-S(O)_2-$. Numerous acid chlorides of Formula $R_4C(O)Cl$, sulfonyl chlorides of Formula $R_4S(O)_2Cl$, and sulfonic anhydrides of Formula $(R_4S(O)_2)_2O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be carried out by adding the acid chloride of Formula $R_4C(O)Cl$, sulfonyl chloride of Formula $R_4S(O)_2Cl$, or sulfonic anhydride of Formula $(R_4S(O)_2)_2O$ to a solution or suspension of a compound of Formula XIVb in a suitable solvent such as chloroform, dichloromethane, *N,N*-dimethylacetamide (DMA), or *N,N*-dimethylformamide (DMF).

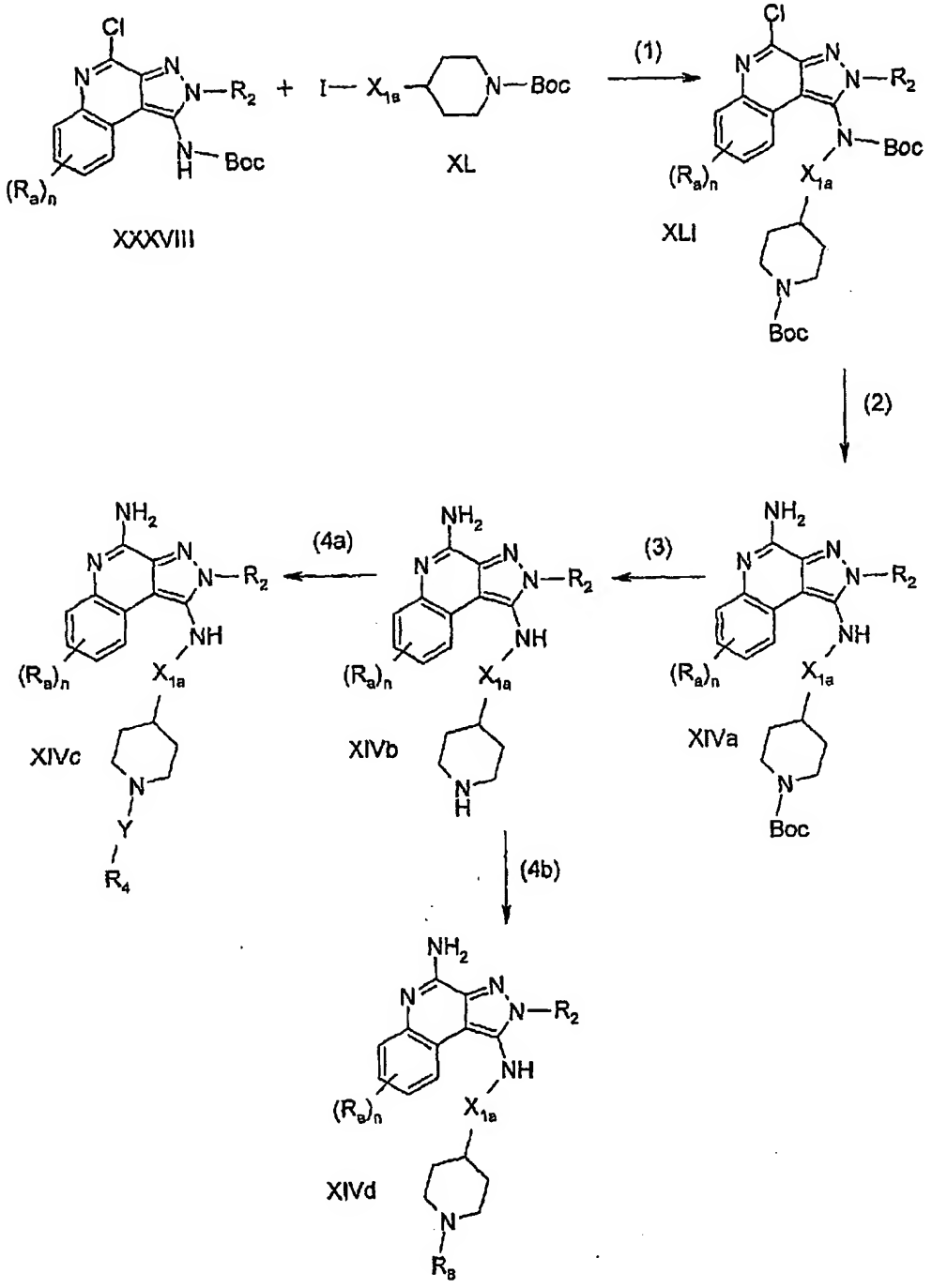
Optionally a base such as triethylamine or *N,N*-diisopropylethylamine can be added. The reaction can be carried out at ambient temperature or at a sub-ambient temperature such as 0 °C.

Ureas of Formula XIVc, where Y is -C(O)-NH- can be prepared by reacting a compound of Formula XIVb or a salt thereof with isocyanates of Formula $R_4N=C=O$. Numerous isocyanates of Formula $R_4N=C=O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be carried out by adding the isocyanate of Formula $R_4N=C=O$ to a solution or suspension of a compound of Formula XIVb in a suitable solvent such as DMA, DMF, or chloroform. Optionally a base such as triethylamine or *N,N*-diisopropylethylamine can be added. The reaction can be carried out at ambient temperature or a sub-ambient temperature such as 0 °C. Alternatively, a compound of Formula XIVb can be treated with a carbamoyl chloride of Formula Cl-C(O)-heterocyclyl, wherein heterocyclyl is attached at a nitrogen atom, to provide a compound of Formula XIVc, wherein Y is -C(O)- and R_4 is heterocyclyl attached at a nitrogen atom.

Sulfamides of Formula XIVc, where Y is $-S(O)_2-N(R_8)-$, can be prepared by reacting a compound or salt of Formula XIVb with sulfuryl chloride to generate a sulfamoyl chloride in situ, and then reacting the sulfamoyl chloride with an amine of Formula $HN(R_8)R_4$. Alternatively, sulfamides of Formula XIVc can be prepared by reacting a compound of Formula XIVb with a sulfamoyl chloride of Formula $R_4(R_8)N-S(O)_2Cl$. Many sulfonyl chlorides of Formula $R_4S(O)_2Cl$ and amines of Formula $HN(R_8)R_4$, and some sulfamoyl chlorides of Formula $R_4(R_8)N-S(O)_2Cl$ are commercially available; others can be prepared using known synthetic methods.

In step (4b) of Reaction Scheme VII, a pyrazolo[3,4-*c*]quinolin-4-amine of Formula XIVb undergoes reductive alkylation to provide a pyrazolo[3,4-*c*]quinolin-4-amine of Formula XIVd. The alkylation can be carried out in two parts by (i) adding an aldehyde or ketone to a solution of a compound of Formula XIVb or a salt thereof in a suitable solvent such as DMF, THF, or methanol in the presence of a base such as *N,N*-diisopropylethylamine. In part (ii) the reduction is carried out by adding a suitable reducing agent such as the borane-pyridine complex. Both part (i) and part (ii) can be carried out at ambient temperature.

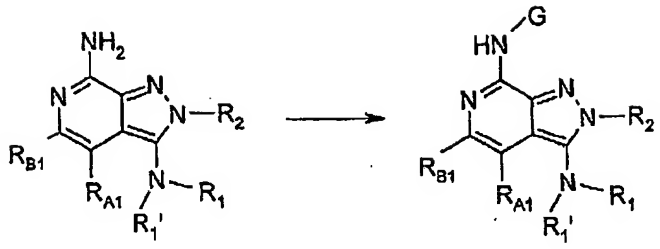
Reaction Scheme VII



In some embodiments, compounds of the invention can be prepared according to Reaction Scheme VIII wherein R_{A1}, R_{B1}, R_1, R_1', R_2, and G are as defined above. The amino group of a compound of Formula II can be converted by conventional methods to a

functional group such as an amide, carbamate, urea, amidine, or another hydrolyzable group. A compound of this type can be made by the replacement of a hydrogen atom in an amino group with a group such as -C(O)-R'", α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R'", -C(O)-N(R'")R'", -C(=NY$_2$)-R'", -CH(OH)-C(O)-OY$_2$, -CH(OC$_{1-4}$ alkyl)Y$_0$, -CH$_2$Y$_1$, and -CH(CH$_3$)Y$_1$; wherein R'" and R'" are independently selected from the group consisting of C$_{1-10}$ alkyl, C$_{3-7}$ cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C$_{1-6}$ alkyl, C$_{1-4}$ alkoxy, aryl, heteroaryl, aryl-C$_{1-4}$ alkylenyl, heteroaryl-C$_{1-4}$ alkylenyl, halo-C$_{1-4}$ alkylenyl, halo-C$_{1-4}$ alkoxy, -O-C(O)-CH$_3$, -C(O)-O-CH$_3$, -C(O)-NH$_2$, -O-CH$_2$-C(O)-NH$_2$, -NH$_2$, and –S(O)$_2$-NH$_2$, with the proviso that R'" can also be hydrogen; each α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids; Y$_2$ is selected from the group consisting of hydrogen, C$_{1-6}$ alkyl, and benzyl; Y$_0$ is selected from the group consisting of C$_{1-6}$ alkyl, carboxy-C$_{1-6}$ alkylenyl, amino-C$_{1-4}$ alkylenyl, mono-*N*-C$_{1-6}$ alkylamino-C$_{1-4}$ alkylenyl, and di-*N*,*N*-C$_{1-6}$ alkylamino-C$_{1-4}$ alkylenyl; and Y$_1$ is selected from the group consisting of mono-*N*-C$_{1-6}$ alkylamino, di-*N*,*N*-C$_{1-6}$ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C$_{1-4}$ alkylpiperazin-1-yl. Particularly useful compounds of Formula XV are amides derived from carboxylic acids containing one to ten carbon atoms, amides derived from amino acids, and carbamates containing one to ten carbon atoms. The reaction can be carried out, for example, by combining a compound of Formula II with a chloroformate or acid chloride, such as ethyl chloroformate or acetyl chloride, in the presence of a base such as triethylamine in a suitable solvent such as dichloromethane at ambient temperature.

Reaction Scheme VIII



Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. The exact amount of compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen.

In some embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject.

In other embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, computed according to the Dubois method, in which the body surface area of a subject (m^2) is computed using the subject's body weight: $m^2 = (wt\ kg^{0.425} \times height\ cm^{0.725}) \times 0.007184$, although in some embodiments the methods may be performed by administering a compound or salt or composition in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound to provide

a dose of from about 0.1 mg/m^2 to about 2.0 mg/ m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like. These dosage forms can be prepared with conventional pharmaceutically acceptable carriers and additives using conventional methods, which generally include the step of bringing the active ingredient into association with the carrier.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts described herein may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts are useful for modulating the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon-α (IFN-α) and tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of the invention to the animal. The animal to which the compound or salt is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to

the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts described herein can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts described herein can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt or composition and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts or compositions identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such as chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, a compound or salt identified herein may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens; toxoids; toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria,

hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts identified herein may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An animal may also be vaccinated by administering an effective amount of a compound or salt described herein, as a vaccine adjuvant. In one embodiment, there is provided a method of vaccinating an animal comprising administering an effective amount of a compound or salt described herein to the animal as a vaccine adjuvant.

An amount of a compound or salt effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased (induced) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, (computed according to the Dubois method as described above) although in some embodiments the induction or inhibition of cytokine biosynthesis may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt or composition to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an

effective amount of a compound or salt of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, (computed according to the Dubois method as described above) although in some embodiments either of these methods may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

In addition to the formulations and uses described specifically herein, other formulations, uses, and administration devices suitable for compounds of the present invention are described in, for example, International Publication Nos. WO 03/077944 and WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2003/0139364, 2003/185835, 2004/0258698, 2004/0265351, 2004/076633, and 2005/0009858.

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

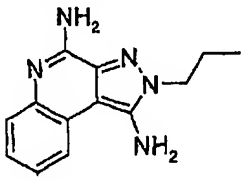
EXAMPLES

In the examples below normal high performance flash chromatography (prep HPLC) was carried out using a HORIZON HPFC system (an automated high-performance flash purification product available from Biotage, Inc, Charlottesville, Virginia, USA) or

an INTELLIFLASH Flash Chromatography System (an automated flash purification system available from AnaLogix, Inc, Burlington, Wisconsin, USA). The eluent used for each purification is given in the example. In some chromatographic separations, the solvent mixture 80/18/2 v/v/v chloroform/methanol/concentrated ammonium hydroxide (CMA) was used as the polar component of the eluent. In these separations, CMA was mixed with chloroform in the indicated ratio.

Example 1

2-Propyl-2*H*-pyrazolo[3,4-c]quinoline-1,4-diamine



Part A

p-Toluenesulfonic acid (2 mg, 0.16 mmol) and acetonylacetone (2.14 g, 18.7 mmol) were added sequentially to a solution of 2-aminophenylacetonitrile (2.06 g, 15.6 mmol) in toluene (30 mL). The reaction mixture was heated in an oil bath at 155°C for 1 hour and then allowed to stand at ambient temperature overnight. Acetonylacetone (0.5 mL) and a small amount of *p*-toluenesulfonic acid were added and the reaction mixture was heated at reflux for 4 hours. The toluene layer was washed sequentially with saturated sodium bicarbonate and water (x2), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to a dark oil. The oil was purified by prep HPLC (AnaLogix, eluted with a gradient of 10-30% ethyl acetate in hexanes) to provide 3.35 g of 2-(2,5-dimethylpyrrol-1-yl)phenylacetonitrile as a pale brown oil.

Part B

2-(2,5-Dimethylpyrrol-1-yl)phenylacetonitrile (15 mmol) and diethyl oxalate (4.38 g, 30 mml) were sequentially added neat washing with ethanol (15 mL) to a solution of sodium *tert*-butoxide (1.73 g, 18 mmol) in ethanol (15 mL). The reaction mixture was heated at reflux under a nitrogen atmosphere for 4.5 hours to provide a solution of ethyl 3-cyano-3-[2-(2,5-dimethylpyrrol-1-yl)phenyl]-2-oxopropionate in ethanol.

Part C

Acetic acid (12 mL) and *n*-propylhydrazine oxalate (985 mg g, 6.0 mmol) were added to a solution of ethyl 3-cyano-3-[2-(2,5-dimethylpyrrol-1-yl)phenyl]-2-oxopropionate in ethanol (6.0 mmol in 12 mL). The reaction mixture was heated in an oil bath at 100°C for 1 hour and then concentrated under reduced pressure. The residue was diluted with 2 M sodium carbonate and then extracted with chloroform. The extract was dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide a black oil. The oil was purified by prep HPLC (AnaLogix, eluted with a gradient of 2 to 50% CMA in chloroform) to provide a brown solid. This material was combined with chloroform and then *tert*-butyl methyl ether was added. A solid was isolated by filtration, washed with *tert*-butyl methyl ether and dried to provide 81 mg of 1-amino-2-propyl-2,5-dihydro-4*H*-pyrazolo[3,4-*c*]quinolin-4-one as a beige solid, mp 266-268°C. MS (APCI) m/z 243 $(M + H)^+$; Anal. Calcd for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.12. Found: C, 64.24; H, 5.86; N, 23.05.

Acetic acid (30 mL) and *n*-propylhydrazine oxalate (9.85 g, 60 mmol) were added to the reaction mixture from Part B, which was then heated at reflux for 2.5 hours. The volatiles were removed under reduced pressure. The residue was made basic with 2 M sodium carbonate and then extracted with chloroform. Water was added to break up the resulting emulsion. The aqueous was back extracted with chloroform. The combined extracts were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide a black resin. Chloroform and hexanes were added sequentially to provide a brown solid. The solid was taken up in a mixture of chloroform and methanol and then filtered to remove a small amount of insoluble material. The filtrate provided 500 mg of material, which was absorbed onto silica gel (5 mL) and then purified by prep HPLC (Biotage, eluted with a gradient of 2-50% CMA in chloroform over 10 column volumes) to provide 184 mg of 1-amino-2-propyl-2,5-dihydro-4*H*-pyrazolo[3,4-*c*]quinolin-4-one as a beige solid. A portion of this material was used in Part D.

Part D

A solution of 1-amino-2-propyl-2,5-dihydro-4*H*-pyrazolo[3,4-*c*]quinolin-4-one (86 mg, 0.36 mmol) in phosphorus oxychloride (3 mL) was heated at 100°C for 45 minutes and then allowed to cool to ambient temperature. The reaction mixture was diluted with

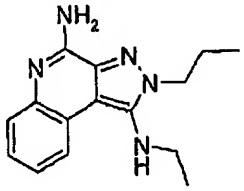
diethyl ether (10 mL). A solid was isolated by filtration, rinsed with diethyl ether, and dried to provide 4-chloro-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-amine.

Part E

The material from Part D was combined with a solution of ammonia in methanol (5 mL of 7 M) in a steel Parr vessel. The vessel was sealed and heated at 150°C for 24 hours and then allowed to stand at ambient temperature for 3 days. The reaction mixture was filtered to remove a precipitate and the filter cake was washed with methanol. The filtrate was absorbed onto silica gel (3 mL) and purified by normal phase prep HPLC (AnaLogix, eluted with a gradient of 5 – 50 % CMA in chloroform) to provide 31 mg of a pale orange solid. This material was refluxed with 75% ethyl acetate in hexanes, isolated by filtration, washed with 50% ethyl acetate in hexanes, and dried to provide about 25 mg of 2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine, mp 253 °C (dec.). Anal. Calcd for: $C_{13}H_{15}N_5 \cdot 0.25\ H_2O$: C, 63.52; H, 6.36; N, 28.50; Found: C, 63.58; H, 5.96; N, 28.50; Duplicate analysis Found: C, 63.30; H, 6.10; N, 28.33.

Example 2

N^1-Ethyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine



Part A

2-Propyl-2,5-dihydro-4*H*-pyrazolo[3,4-*c*]quinolin-4-one was prepared from ethyl 1*H*-indol-3-yl(oxo)acetate and propylhydrazine oxalate according to the general procedure in the literature (Catarzi, D.; Colotta, V.; Varano, F.; Cecchi, L.; Filacchioni, G.; Galli, A.; Costagli, C. *Arch. Pharm. Pharm. Med. Chem.* 1997, *330*, 383-386.).

Part B

A 12 L reaction vessel was charged with 2-propyl-2,5-dihydro-4*H*-pyrazolo[3,4-*c*]quinolin-4-one (103.40 g, 455 mmol), tetrahydrofuran (THF, 6.1 L), and *N,N,N',N'*-tetramethylethylenediamine (392 mL, 2.59 mol), and the resulting suspension was cooled in an ice bath. *n*-Butyllithium (510 mL of a 2.5 M solution in hexane, 1.27 mol) was added over 65 minutes, and the reaction was allowed to stir at 5 °C for 20 minutes. The

contents of the 12 L vessel were transferred via cannula over a period of 20 minutes to a 22 L vessel containing dry ice (3 kg) and diethyl ether (2 L). The reaction was stirred overnight, water (3 L) was added, the organic layer was drawn off, and the aqueous layer was washed with chloroform (4 x 500 mL). The aqueous layer was acidified by treatment with 2 M HCl (1.6 L), and the resulting suspension was stirred overnight. The solid was collected by filtration and dried on suction for 2 days to afford 69.47 g of 4-oxo-2-propyl-4,5-dihydro-2*H*-pyrazolo[3,4-*c*]quinoline-1-carboxylic acid as an off-white solid.

Part C

4-Oxo-2-propyl-4,5-dihydro-2*H*-pyrazolo[3,4-*c*]quinoline-1-carboxylic acid (20 g, 73.7 mmol) was boiled in thionyl chloride (100 mL) and toluene (100 mL) for 7 hours. A small amount of insoluble powder was removed by filtration, and the filtrate was concentrated, treated with toluene and concentrated (2x), then dissolved in acetone (250 mL). The resulting solution was cooled in an ice bath, and a solution of sodium azide (15.3 g, 235 mmol) in water (40 mL) was added in one portion. The cooling bath was removed, the reaction was stirred for 15 minutes more, and water (700 mL) was added to precipitate the product. The solid was collected by filtration, washed with water, dried briefly on suction, and transferred to a round-bottomed flask as a suspension in toluene. The toluene was removed at 30 °C under vacuum, and the solid was concentrated from toluene twice more. Toluene (200 mL) and *tert*-butanol (10 g, 135 mmol) were added, and the mixture was heated to reflux for 30 minutes. Some insoluble material was removed by filtration, and the contents of the filtrate were purified by prep HPLC (silica cartridge, eluting with 35% to 45% ethyl acetate in hexane). The resulting yellow foam was recrystallized from 25% ethyl acetate in hexane (100 mL) to afford 16.29 g of *tert*-butyl 4-chloro-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-ylcarbamate as a pale yellow powder.

Part D

To a solution of *tert*-butyl 4-chloro-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-ylcarbamate (722 mg, 2.00 mmol) in THF (5 mL) was added ethyl iodide (624 mg, 4.0 mmol). Sodium hydride (120 mg of a 60 wt% dispersion in mineral oil, 3.00 mmol) was added, and after 40 min, more ethyl iodide (624 mg, 2.00 mmol) was added, and the reaction was stirred overnight. Saturated ammonium chloride was added, and the aqueous layer was extracted with methyl *tert*-butyl ether (3x). The combined organic layers were

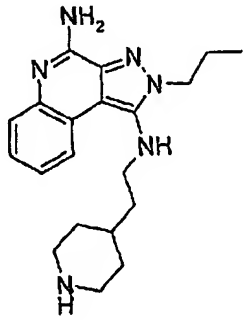
dried (magnesium sulfate), filtered, concentrated, and purified by prep HPLC (silica cartridge, eluting with ethyl acetate in hexane) to afford 718 mg of *tert*-butyl 4-chloro-2-propyl-2*H*-pyrazolo[3,4-c]quinolin-1-yl(ethyl)carbamate as a white solid.

Part E

tert-Butyl 4-chloro-2-propyl-2*H*-pyrazolo[3,4-c]quinolin-1-yl(ethyl)carbamate (718 mg, 1.85 mmol) and methanolic ammonia (25 mL of a 7 M solution) were heated in a steel Parr vessel in a 150 °C oven for 17 h. The reaction mixture was concentrated, treated with 2 M sodium carbonate and extracted with chloroform. The combined organic layers were dried (magnesium sulfate), filtered, concentrated, and purified by prep HPLC (silica cartridge, eluting with CMA in chloroform). The product was recrystallized from acetonitrile to afford 272 mg of N^1-ethyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine as white crystals, mp 193-194 °C. MS (APCI) m/z 270 $(M + H)^+$; Anal. Calcd for $C_{15}H_{19}N_5$: C, 66.89; H, 7.11; N, 26.00. Found: C, 66.65; H, 7.20; N, 26.19.

Example 3

N^1-(2-piperidin-4-ylethyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine



Part A

tert-Butyl 4-(2-iodoethyl)piperidine-1-carboxylate (9.87 g, 29.1 mmol) was added to a solution of butyl 4-chloro-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-ylcarbamate (7.0 g, 19.4 mmol) in THF (100 mL). Sodium hydride (60 % in mineral oil, 1.16 g, 29.1 mmol) was added and the reaction mixture was heated at reflux for 16 hours. Saturated ammonium chloride (100 mL) was slowly added and then the mixture was extracted with methyl *tert*-butyl ether (2 x 100 mL). The combined organics were dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide a thick oil. The oil was purified by prep HPLC (silica gel eluted with a linear gradient of 0 to 15% CMA

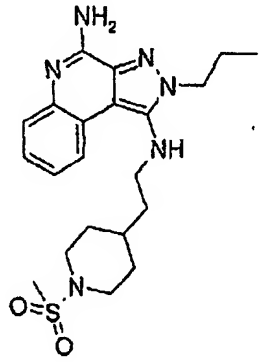
in chloroform, 2800 mL) to provide 9.52 g of *tert*-butyl 4-{2-[(*tert*-butoxycarbonyl)(4-chloro-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)amino]ethyl}piperidine-1-carboxylate as a white foam.

Part B

A solution of *tert*-butyl 4-{2-[(*tert*-butoxycarbonyl)(4-chloro-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)amino]ethyl}piperidine-1-carboxylate (1.41 g) in 7N ammonia in methanol (25 mL) was placed in a stainless steel pressure vessel and heated at 150 °C for 18 hours. The reaction mixture was cooled to ambient temperature and then concentrated under reduced pressure to provide a brown residue. The residue was suspended in anhydrous ethanol (20 mL). Hydrochloric acid (4 mL of 3M) was added and the reaction mixture was heated at reflux for 4 hours. The reaction mixture was concentrated under reduced pressure. The residue was triturated with diethyl ether and the resulting solid was isolated by filtration to provide 0.7 g of N^1-(2-piperidin-4-ylethyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine dihydrochloride as a brown solid. MS (APCI) m/z 353.30 $(M + H)^+$. The experiment was repeated using 5.75 g of *tert*-butyl 4-{2-[(*tert*-butoxycarbonyl)(4-chloro-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)amino]ethyl}piperidine-1-carboxylate in 70 mL of 7N ammonia in methanol followed by treatment with 16.75 mL of 3M hydrochloric acid to provide 4.1 g of product as a brown solid. MS (APCI) m/z 353.26 $(M + H)^+$.

Example 4

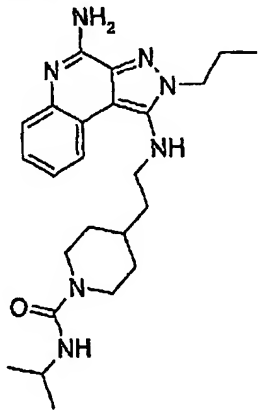
N^1-{2-[1-(Methylsulfonyl)piperidin-4-yl]ethyl}-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine



Methanesulfonyl chloride (0.30 g, 0.20 mL, 2.58 mmol) was added to a stirring suspension of N^1-(2-piperidin-4-ylethyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine dihydrochloride (1.0 g, 2.35 mmol) and triethylamine (0.59 g, 0.82 mL, 5.88 mmol) in dichloromethane (10 mL). The resulting suspension was stirred at ambient temperature 16 hours. Additional dichloromethane (90 mL), triethylamine (4.2 g, 5.7 mL, 41.1 mmol) and methanesulfonyl chloride (0.19 g, 0.13 mL, 1.66 mmol) were added to the mixture and the resulting cloudy suspension was stirred at ambient temperature 3 days. The reaction mixture was concentrated and the resulting brown solid was purified by column chromatography using a HORIZON HPFC system (silica cartridge, eluting with 5 – 20% methanol in dichloromethane). The resulting oil was crystallized from acetonitrile and isolated by filtration to yield 169 mg of N^1-{2-[1-(methylsulfonyl)piperidin-4-yl]ethyl}-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine as an off-white solid, mp 204-207 °C. Anal. calcd for $C_{21}H_{30}N_6O_2S$: C, 58.58; H, 7.02; N, 19.52. Found: C, 58.77; H, 6.92; N, 19.54.

Example 5

4-{2-[(4-Amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)amino]ethyl}-*N*-isopropylpiperidine-1-carboxamide

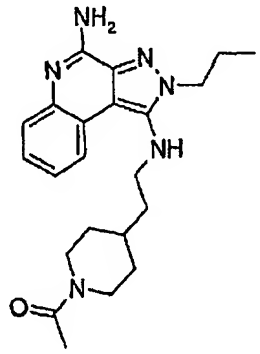


Isopropyl isocyanate (0.29 g, 0.33 mL, 3.39 mmol) was added to a stirring suspension of N^1-(2-piperidin-4-ylethyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine dihydrochloride (1.2 g, 2.83 mmol) and triethylamine (2.9 g, 3.9 mL, 28.3 mmol) in dichloromethane (100 mL). After 10 minutes, *N*,*N*-dimethylformamide (15 mL) was added and the resulting suspension was stirred at ambient temperature 16 hours. The

dichloromethane was removed under reduced pressure and water (100 mL) was added to the resulting oil. A solid formed which was removed by filtration and discarded. The filtrate was transferred to a separatory funnel and extracted with dichloromethane (50 mL). The aqueous layer was saturated with solid sodium bicarbonate and extracted with dichloromethane (3 x 50 mL). The organic fractions were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting brown oil was purified by column chromatography using a HORIZON HPFC system (silica cartridge, eluting with 3 – 15% methanol in dichloromethane). The resulting oil was crystallized from acetonitrile and isolated by filtration to yield 132 mg of 4-{2-[(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)amino]ethyl}-*N*-isopropylpiperidine-1-carboxamide as a white solid, mp 168-170 °C. Anal. calcd for $C_{24}H_{35}N_7O$: C, 65.88; H, 8.06; N, 22.41. Found: C, 65.89; H, 8.24; N, 22.67.

Example 6

N^1-[2-(1-Acetylpiperidin-4-yl)ethyl]-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine

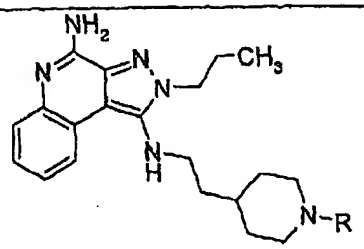


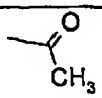
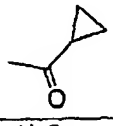
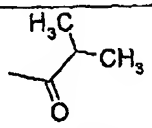
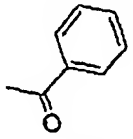
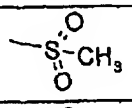
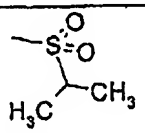
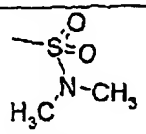
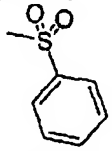
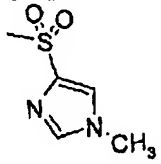
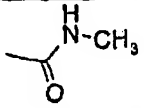
Acetyl chloride (0.27 g, 0.24 mL, 3.39 mmol) was added to a stirring suspension of N^1-(2-piperidin-4-ylethyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine dihydrochloride (1.2 g, 2.83 mmol) and triethylamine (2.9 g, 3.9 mL, 28.3 mmol) in dichloromethane (100 mL). After 10 minutes, 1-methyl-2-pyrrolidinone (15 mL) was added and the resulting suspension was stirred at ambient temperature 16 hours. Additional acetyl chloride (0.27 g, 0.24 mL, 3.39 mmol) was added and the suspension was stirred at ambient temperature 4 hours. The dichloromethane was removed under reduced pressure and water (100 mL) was added to the resulting oil. The solution was transferred to a separatory funnel and extracted with ethyl acetate (2 x 50 mL) and

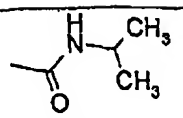
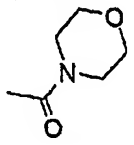
dichloromethane (50 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Methanol (20 mL) and sodium hydroxide (10 mL, 1 N in water) were added to the resulting oil and the suspension was stirred one hour. The methanol was removed under reduced pressure and the aqueous layer was neutralized with hydrochloric acid (1 N in water) and extracted with dichloromethane (3 x 50 mL). The combined organic fractions were dried over magnesium sulfate, filtered and concentrated under reduced pressure to 7.5 g of a yellow oil. Sodium carbonate (75 mL, 10% w/w in water) was added to this oil and a brown gum crashed out and stuck to the sides of the flask. The liquid was decanted off and the remaining gum was crystallized from hot acetonitrile (50 mL) and isolated by filtration to yield 242 mg of *N*^{1}-[2-(1-acetylpiperidin-4-yl)ethyl]-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine as a tan solid. mp 203-206 °C. Anal. calcd for $C_{22}H_{30}N_6O$: C, 66.98; H, 7.66; N, 21.30. Found: C, 66.92; H, 7.92; N, 21.57.

Examples 7 – 18

N^1-(2-piperidin-4-ylethyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine dihydrochloride (700 mg) was combined with *N,N*-diisopropylethylamine (1.4 mL) and sufficient *N,N*-dimethylacetamide to provide a total volume of 16 mL. A portion (1.0 ml) was added to a tube containing a reagent (1.1 eq) from the table below. The reaction mixture was stirred overnight and then quenched with water (100 µL). The solvent was removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography using a Waters FractionLynx automated purification system. The fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. Fractions were collected by mass-selective triggering. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

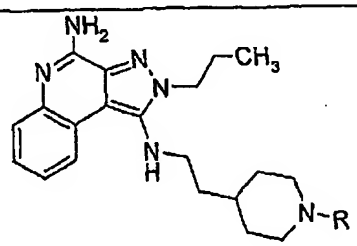


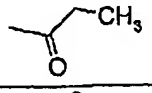
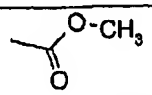
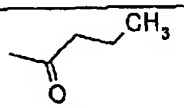
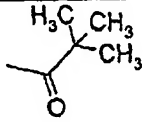
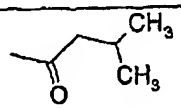
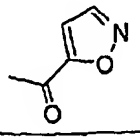
Example	Reagent	R	Measured Mass (M+H)
7	Acetyl chloride		395.2530
8	Cyclopropanecarbonyl chloride		421.2685
9	Isobutyryl chloride		423.2836
10	Benzoyl chloride		457.2716
11	Methanesulfonyl chloride		431.2207
12	Isopropylsulfonyl chloride		459.2543
13	Dimethylsulfamoyl chloride		460.2489
14	Benzenesulfonyl chloride		493.2383
15	1-Methylimidazole-4-sulfonyl chloride		497.2431
16	Methyl isocyanate		410.2664

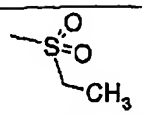
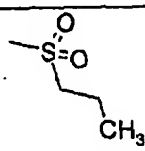
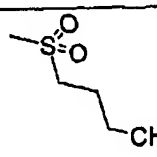
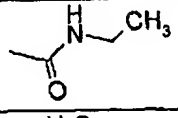
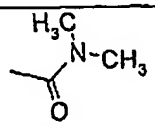
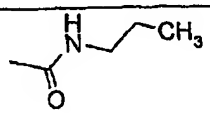
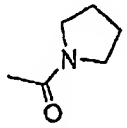
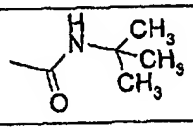
17	Isopropyl isocyanate		438.2970
18	4-Morpholinylcarbonyl chloride		466.2916

Examples 19 – 32

The compounds in the table below were prepared and purified according to the general method of Examples 7 – 18 except that the reaction mixtures were stirred for 4 hours instead of overnight. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

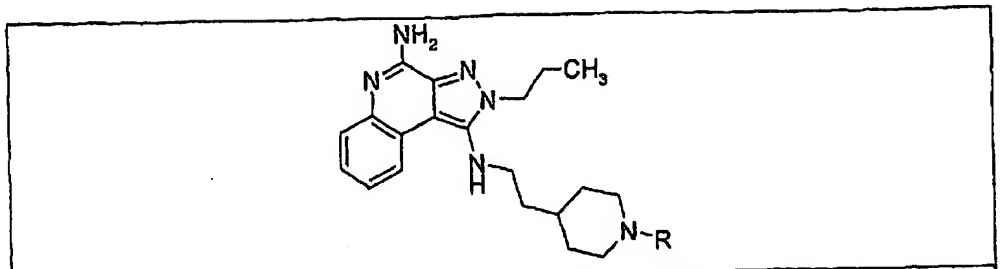


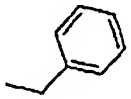
Example	Reagent	R	Measured Mass (M+H)
19	Propionyl chloride		409.2676
20	Methyl chloroformate		411.2481
21	Butyryl chloride		423.2859
22	Pivaloyl chloride		437.3002
23	Isovaleryl chloride		437.3009
24	Isoxazole-5-carbonyl chloride		448.2429

25	Ethanesulfonyl chloride		445.2346
26	1-Propanesulfonyl chloride		459.2499
27	1-Butanesulfonyl chloride		473.2683
28	Ethyl isocyanate		424.2790
29	*N,N*-Dimethylcarbamoyl chloride		424.2794
30	*N*-Propyl isocyanate		438.2968
31	1-Pyrrolidinecarbonyl chloride		450.2959
32	*tert*-Butyl isocyanate		452.3105

Examples 33 and 34

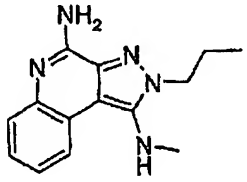
N^1-(2-piperidin-4-ylethyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine dihydrochloride (468 mg) was combined with *N,N*-diisopropylethylamine (383 µL) and sufficient methanol to provide a total volume of 11 mL. A portion (1.0 ml) was added to a tube containing a reagent (1.25 eq) from the table below. The reaction mixture was stirred for 15 minutes. Borane-pyridine complex (16 µL) was added and the reaction mixture was stirred for 4 hours. The solvent was removed by vacuum centrifugation and the compound was purified according to the method described in Examples 7 – 18. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)
33	2-Hydroxyacetaldehyde		397.2685
34	Benzaldehyde		443.2899

Example 35

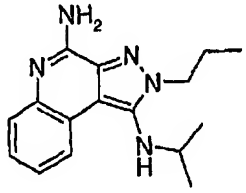
N^1-Methyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine



N^1-Methyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine was prepared according to the general methods of Example 2 using methyl iodide in lieu of ethyl iodide in Part D. The product was provided as white crystals, mp 200-201 °C. MS (APCI) m/z 256 $(M + H)^+$; Anal. Calcd for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43. Found: C, 66.07; H, 6.50; N, 27.81.

Example 36

N^1-Isopropyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine

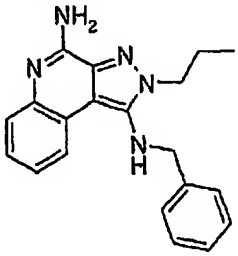


N^1-Isopropyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine diamine was prepared according to the general methods of Example 2 using 2-iodopropane in lieu of

ethyl iodide in Part D. The product was provided as a white solid, mp 199-200 °C. MS (APCI) m/z 284 $(M + H)^+$; Anal. Calcd for $C_{16}H_{21}N_5$: C, 67.82; H, 7.47; N, 24.71. Found: C, 67.60; H, 7.58; N, 24.77.

Example 37

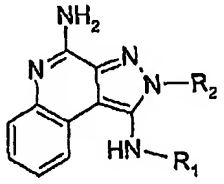
N^1-Benzyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine



N^1-Benzyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-1,4-diamine was prepared according to the general methods of Example 2 using benzyl bromide in lieu of ethyl iodide in Part D. The product was provided as a pale yellow solid, mp 160-161 °C. MS (APCI) m/z 332 $(M + H)^+$; Anal. Calcd for $C_{20}H_{21}N_5$: C, 72.48; H, 6.39; N, 21.13. Found: C, 72.71; H, 6.57; N, 21.25.

Exemplary Compounds

Certain exemplary compounds, including some of those described above in the Examples, have the following Formula IVj and the following R_1 and R_2 substituents, wherein each line of the table is matched with Formula IVj to represent a specific embodiment of the invention.



IVj

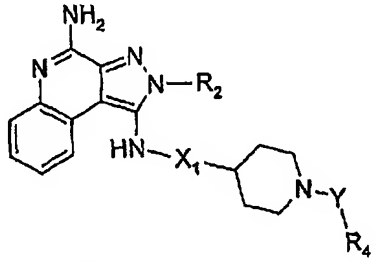
R_1	R_2
methyl	methyl
methyl	ethyl

methyl	*n*-propyl
methyl	*n*-butyl
methyl	2-methoxyethyl
methyl	2-hydroxyethyl
ethyl	methyl
ethyl	ethyl
ethyl	*n*-propyl
ethyl	*n*-butyl
ethyl	2-methoxyethyl
ethyl	2-hydroxyethyl
n-propyl	methyl
n-propyl	ethyl
n-propyl	*n*-propyl
n-propyl	*n*-butyl
n-propyl	2-methoxyethyl
n-propyl	2-hydroxyethyl
1-methylethyl	methyl
1-methylethyl	ethyl
1-methylethyl	*n*-propyl
1-methylethyl	*n*-butyl
1-methylethyl	2-methoxyethyl
1-methylethyl	2-hydroxyethyl
n-butyl	methyl
n-butyl	ethyl
n-butyl	*n*-propyl
n-butyl	*n*-butyl
n-butyl	2-methoxyethyl
n-butyl	2-hydroxyethyl
1-ethylpropyl	methyl
1-ethylpropyl	ethyl
1-ethylpropyl	*n*-propyl

1-ethylpropyl	*n*-butyl
1-ethylpropyl	2-methoxyethyl
1-ethylpropyl	2-hydroxyethyl
2-methylpropyl	methyl
2-methylpropyl	ethyl
2-methylpropyl	*n*-propyl
2-methylpropyl	*n*-butyl
2-methylpropyl	2-methoxyethyl
2-methylpropyl	2-hydroxyethyl
3-methylbutyl	methyl
3-methylbutyl	ethyl
3-methylbutyl	*n*-propyl
3-methylbutyl	*n*-butyl
3-methylbutyl	2-methoxyethyl
3-methylbutyl	2-hydroxyethyl
benzyl	methyl
benzyl	ethyl
benzyl	*n*-propyl
benzyl	*n*-butyl
benzyl	2-methoxyethyl
benzyl	2-hydroxyethyl
2-phenylethyl	methyl
2-phenylethyl	ethyl
2-phenylethyl	*n*-propyl
2-phenylethyl	*n*-butyl
2-phenylethyl	2-methoxyethyl
2-phenylethyl	2-hydroxyethyl
3-phenylpropyl	methyl
3-phenylpropyl	ethyl
3-phenylpropyl	*n*-propyl
3-phenylpropyl	*n*-butyl

3-phenylpropyl	2-methoxyethyl
3-phenylpropyl	2-hydroxyethyl

Certain exemplary compounds, including some of those described above in the Examples, have the following Formula XIVe and the following R_2, X_1, and -Y-R_4 substituents, wherein each line of the table is matched with Formula XIVe to represent a specific embodiment of the invention.



XIVe

X_1	-Y-R_4	R_2
-CH_2-	-C(O)-CH_3	methyl
-CH_2-	-C(O)-CH_3	ethyl
-CH_2-	-C(O)-CH_3	*n*-propyl
-CH_2-	-C(O)-CH_3	*n*-butyl
-CH_2-	-C(O)-CH_3	2-methoxyethyl
-CH_2-	-C(O)-CH_3	2-hydroxyethyl
-CH_2-	-S(O)$_2$-CH_3	methyl
-CH_2-	-S(O)$_2$-CH_3	ethyl
-CH_2-	-S(O)$_2$-CH_3	*n*-propyl
-CH_2-	-S(O)$_2$-CH_3	*n*-butyl
-CH_2-	-S(O)$_2$-CH_3	2-methoxyethyl
-CH_2-	-S(O)$_2$-CH_3	2-hydroxyethyl
-CH_2-	-C(O)-NH-CH(CH_3)$_2$	methyl
-CH_2-	-C(O)-NH-CH(CH_3)$_2$	ethyl
-CH_2-	-C(O)-NH-CH(CH_3)$_2$	*n*-propyl

$-CH_2-$	$-C(O)-NH-CH(CH_3)_2$	*n*-butyl
$-CH_2-$	$-C(O)-NH-CH(CH_3)_2$	2-methoxyethyl
$-CH_2-$	$-C(O)-NH-CH(CH_3)_2$	2-hydroxyethyl
$-CH_2CH_2-$	$-C(O)-CH_3$	methyl
$-CH_2CH_2-$	$-C(O)-CH_3$	ethyl
$-CH_2CH_2-$	$-C(O)-CH_3$	*n*-propyl
$-CH_2CH_2-$	$-C(O)-CH_3$	*n*-butyl
$-CH_2CH_2-$	$-C(O)-CH_3$	2-methoxyethyl
$-CH_2CH_2-$	$-C(O)-CH_3$	2-hydroxyethyl
$-CH_2CH_2-$	$-S(O)_2-CH_3$	methyl
$-CH_2CH_2-$	$-S(O)_2-CH_3$	ethyl
$-CH_2CH_2-$	$-S(O)_2-CH_3$	*n*-propyl
$-CH_2CH_2-$	$-S(O)_2-CH_3$	*n*-butyl
$-CH_2CH_2-$	$-S(O)_2-CH_3$	2-methoxyethyl
$-CH_2CH_2-$	$-S(O)_2-CH_3$	2-hydroxyethyl
$-CH_2CH_2-$	$-C(O)-NH-CH(CH_3)_2$	methyl
$-CH_2CH_2-$	$-C(O)-NH-CH(CH_3)_2$	ethyl
$-CH_2CH_2-$	$-C(O)-NH-CH(CH_3)_2$	*n*-propyl
$-CH_2CH_2-$	$-C(O)-NH-CH(CH_3)_2$	*n*-butyl
$-CH_2CH_2-$	$-C(O)-NH-CH(CH_3)_2$	2-methoxyethyl
$-CH_2CH_2-$	$-C(O)-NH-CH(CH_3)_2$	2-hydroxyethyl

Compounds of the invention have been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α in human cells when tested using one of the methods described below.

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN-α and TNF-α, respectively) secreted into culture media as described by Testerman et. al. in

"Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, *58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (usually 30-0.014 μM). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for IFN-α by ELISA and for TNF-α by IGEN/BioVeris Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis

IFN-α concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

The TNF-α concentration is determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF-α capture and detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α and IFN-α (y-axis) as a function of compound concentration (x-axis).

Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. If any negative values result from background subtraction, the reading is reported as " * ", and is noted as not reliably detectable. In subsequent calculations and statistics, " * ", is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on the past 61 experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784;

Example 91) and the expected area is the sum of the median dose values from the past 61 experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

CYTOKINE INDUCTION IN HUMAN CELLS

(High Throughput Screen)

The CYTOKINE INDUCTION IN HUMAN CELLS test method described above was modified as follows for high throughput screening.

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4 x 10^6 cells/mL in RPMI complete (2-fold the final cell density). The PBMC suspension is added to 96-well flat bottom sterile tissue culture plates.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The compounds are generally tested at concentrations ranging from 30 - 0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with a reference compound 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1H-imidazo[4,5-c]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) on each plate. The solution of test compound is added at 7.5 mM to the first well of a

dosing plate and serial 3 fold dilutions are made for the 7 subsequent concentrations in DMSO. RPMI Complete media is then added to the test compound dilutions in order to reach a final compound concentration of 2-fold higher (60 - 0.028 μM) than the final tested concentration range.

Incubation

Compound solution is then added to the wells containing the PBMC suspension bringing the test compound concentrations to the desired range (usually 30 - 0.014 μM) and the DMSO concentration to 0.4 %. The final concentration of PBMC suspension is $2x10^6$ cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 g) at 4°C. 4-plex Human Panel MSD MULTI-SPOT 96-well plates are pre-coated with the appropriate capture antibodies by MesoScale Discovery, Inc. (MSD, Gaithersburg, MD). The cell-free culture supernatants are removed and transferred to the MSD plates. Fresh samples are typically tested, although they may be maintained at -30 to -70°C until analysis.

Interferon-α and Tumor Necrosis Factor-α Analysis

MSD MULTI-SPOT plates contain within each well capture antibodies for human TNF-α and human IFN-α that have been pre-coated on specific spots. Each well contains four spots: one human TNF-α capture antibody (MSD) spot, one human IFN- α capture antibody (PBL Biomedical Laboratories, Piscataway, NJ) spot, and two inactive bovine serum albumin spots. The human TNF-α capture and detection antibody pair is from MesoScale Discovery. The human IFN-α multi-subtype antibody (PBL Biomedical Laboratories) captures all IFN-α subtypes except IFN-α F (IFNA21). Standards consist of recombinant human TNF-α (R&D Systems, Minneapolis, MN) and IFN-α (PBL Biomedical Laboratories). Samples and separate standards are added at the time of analysis to each MSD plate. Two human IFN-α detection antibodies (Cat. Nos. 21112 & 21100, PBL) are used in a two to one ratio (weight:weight) to each other to determine the

IFN-α concentrations. The cytokine-specific detection antibodies are labeled with the SULFO-TAG reagent (MSD). After adding the SULFO-TAG labeled detection antibodies to the wells, each well's electrochemoluminescent levels are read using MSD's SECTOR HTS READER. Results are expressed in pg/mL upon calculation with known cytokine standards.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α or IFN-α (y-axis) as a function of compound concentration (x-axis).

A plate-wise scaling is performed within a given experiment aimed at reducing plate-to-plate variability associated within the same experiment. First, the greater of the median DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. Negative values that may result from background subtraction are set to zero. Each plate within a given experiment has a reference compound that serves as a control. This control is used to calculate a median expected area under the curve across all plates in the assay. A plate-wise scaling factor is calculated for each plate as a ratio of the area of the reference compound on the particular plate to the median expected area for the entire experiment. The data from each plate are then multiplied by the plate-wise scaling factor for all plates. Only data from plates bearing a scaling factor of between 0.5 and 2.0 (for both cytokines IFN-α, TNF-α) are reported. Data from plates with scaling factors outside the above mentioned interval are retested until they bear scaling factors inside the above mentioned interval. The above method produces a scaling of the y-values without altering the shape of the curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91). The median expected area is the median area across all plates that are part of a given experiment.

A second scaling may also be performed to reduce inter-experiment variability (across multiple experiments). All background-subtracted values are multiplied by a single adjustment ratio to decrease experiment-to-experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on an average of previous experiments (unadjusted

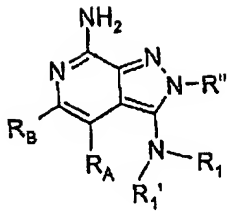
readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from an average of previous experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of the Formula I:



I

wherein:

R_1 is selected from the group consisting of:

$-R_4$,

$-Y-R_4$,

$-X-N(R_8)-Y-R_4$,

$-X-C(R_6)-N(R_8)-R_4$,

$-X-O-C(R_6)-N(R_8)-R_4$,

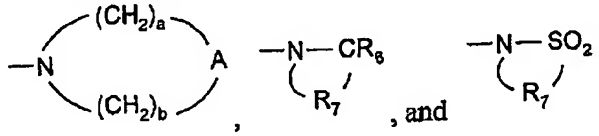
$-X-S(O)_2-N(R_8)-R_4$,

$-X-O-R_4$, and

$-X-R_5$;

R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

or R_1 and R_1' together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



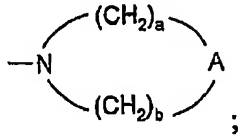
, and ;

A is selected from the group consisting of $-CH(R_8)-$, $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, and $-N(X-N(R_8)-Y-R_4)-$;

X is C_{2-20} alkylene;

Y is selected from the group consisting of $-C(R_6)-$, $-C(R_6)-O-$, $-S(O)_2-$,

$-S(O)_2-N(R_8)-$, and $-C(R_6)-N(R_{11})-$; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group



;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, $-N(R_8)-$, $-N(Y-R_4)-$, or $-N(X-N(R_8)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

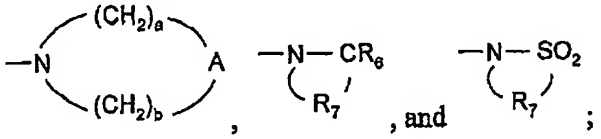
alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

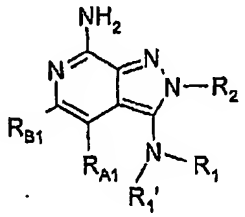
R_9 is selected from the group consisting of hydrogen and alkyl;

R' is a non-interfering substituent; and

R" is hydrogen or a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

2. A compound of the Formula II:



II

wherein:

R_1 is selected from the group consisting of:

$-R_4$,

$-Y-R_4$,

$-X-N(R_8)-Y-R_4$,

$-X-C(R_6)-N(R_8)-R_4$,

$-X-O-C(R_6)-N(R_8)-R_4$,

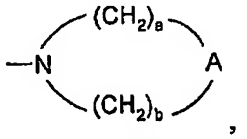
$-X-S(O)_2-N(R_8)-R_4$,

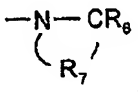
$-X-O-R_4$, and

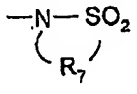
$-X-R_5$;

R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

or R_1 and R_1' together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



,


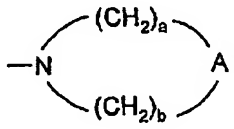
, and


;

A is selected from the group consisting of $-CH(R_8)-$, $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, and $-N(X-N(R_8)-Y-R_4)-$;

X is C_{2-20} alkylene;

Y is selected from the group consisting of $-C(R_6)-$, $-C(R_6)-O-$, $-S(O)_2-$, $-S(O)_2-N(R_8)-$, and $-C(R_6)-N(R_{11})-$; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group



;

a and b are independently integers from 1 to 4 with the proviso that when A is $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, or $-N(X-N(R_8)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4'$,
$-X'-R_4'$,
$-X'-Y'-R_4'$, and
$-X'-R_5'$;

R_3 is selected from the group consisting of:

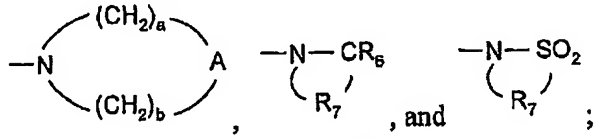
$-Z-R_4'$,
$-Z-X'-R_4'$,
$-Z-X'-Y'-R_4'$,
$-Z-X'-Y'-X'-Y'-R_4'$, and

-Z-X'-R_5';

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

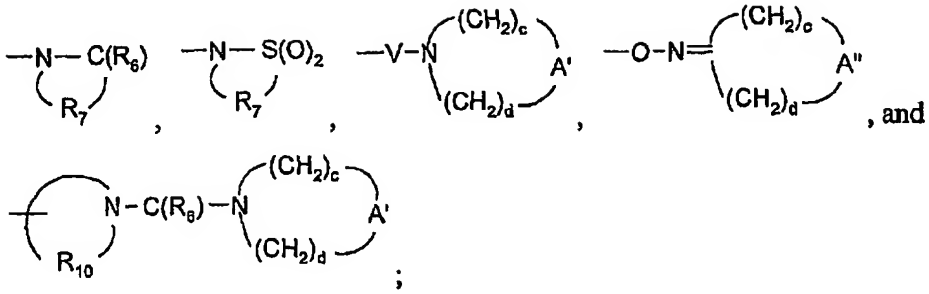
R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



, , and ;

R_5' is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A' is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, and -$N(R_4)$-;

A" is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and -$S(O)_2$-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

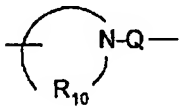
-$C(R_6)$-O-,

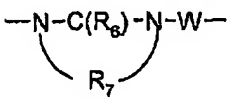
-O-$C(R_6)$-,

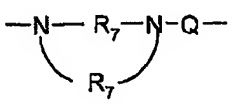
-O-C(O)-O-,

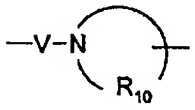
-$N(R_8)$-Q-,

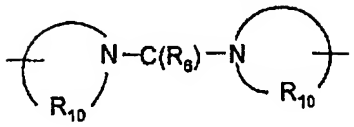
-C(R_6)-N(R_8)-,
-O-C(R_6)-N(R_8)-,
-C(R_6)-N(OR_9)-,
-O-N(R_8)-Q-,
-O-N=C(R_4)-,
-C(=N-O-R_8)-,
-CH(-N(-O-R_8)-Q-R_4)-,


,


,


,


, and

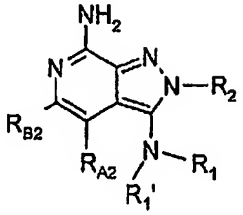

;

Z is a bond or -O-; and

c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7;

or a pharmaceutically acceptable salt thereof.

3. A compound of the Formula III:



III

wherein:

R_1 is selected from the group consisting of:

$-R_4$,

$-Y-R_4$,

$-X-N(R_8)-Y-R_4$,

$-X-C(R_6)-N(R_8)-R_4$,

$-X-O-C(R_6)-N(R_8)-R_4$,

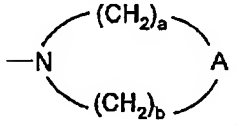
$-X-S(O)_2-N(R_8)-R_4$,

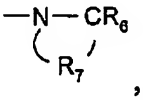
$-X-O-R_4$, and

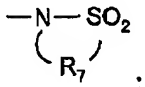
$-X-R_5$;

R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

or R_1 and R_1' together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



,


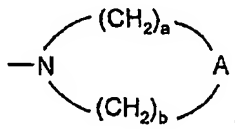
, and


;

A is selected from the group consisting of $-CH(R_8)-$, $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, and $-N(X-N(R_8)-Y-R_4)-$;

X is C_{2-20} alkylene;

Y is selected from the group consisting of $-C(R_6)-$, $-C(R_6)-O-$, $-S(O)_2-$, $-S(O)_2-N(R_8)-$, and $-C(R_6)-N(R_{11})-$; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group



;

a and b are independently integers from 1 to 4 with the proviso that when A is $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, or $-N(X-N(R_8)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

R_{A2} and R_{B2} are each independently selected from the group consisting of:

hydrogen,

halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

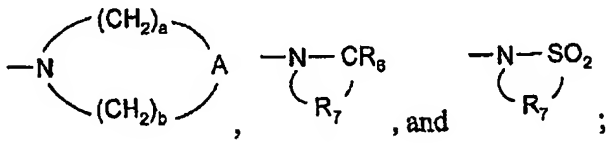
R_2 is selected from the group consisting of:
$-R_4'$,
$-X'-R_4'$,
$-X'-Y'-R_4'$, and
$-X'-R_5'$;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino,

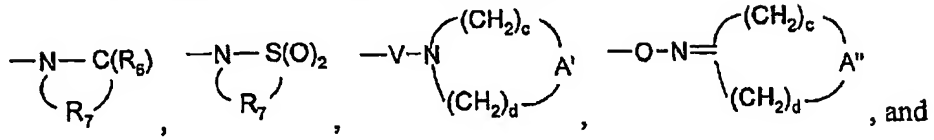
(dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

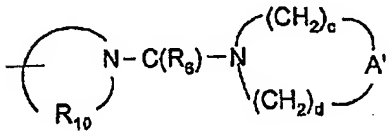
R_5 is selected from the group consisting of:



;

R_5' is selected from the group consisting of:





;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A' is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A" is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

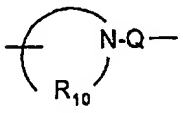
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

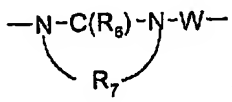
$-O-N=C(R_4)-$,

$-C(=N-O-R_8)-$,

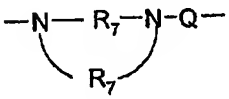
$-CH(-N(-O-R_8)-Q-R_4)-$,



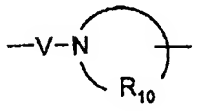
,



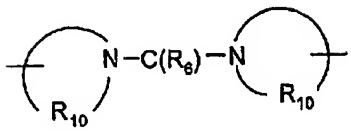
,



,



, and

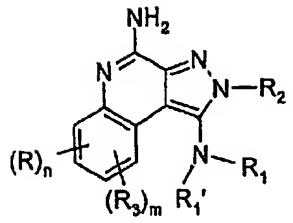


; and

c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7;

or a pharmaceutically acceptable salt thereof.

4. A compound of the Formula IV:



IV

wherein:

R_1 is selected from the group consisting of:

-R_4,

-Y-R_4,

-X-N(R_8)-Y-R_4,

-X-C(R_6)-N(R_8)-R_4,

-X-O-C(R_6)-N(R_8)-R_4,

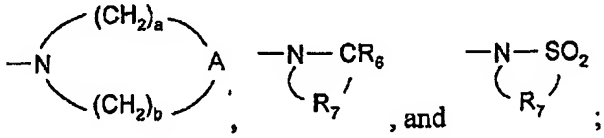
-X-S(O)$_2$-N(R_8)-R_4,

-X-O-R_4, and

-X-R_5;

R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

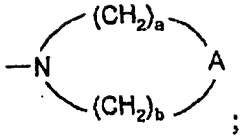
or R_1 and R_1' together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



A is selected from the group consisting of -CH(R_8)-, -O-, -N(R_8)-, -N(Y-R_4)-, and -N(X-N(R_8)-Y-R_4)-;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -C(R_6)-, -C(R_6)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_8)-, and -C(R_6)-N(R_{11})-; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group



;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -N(R_8)-, -N(Y-R_4)-, or -N(X-N(R_8)-Y-R_4)- then a and b are independently integers from 2 to 4;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

n is an integer from 0 to 4;

R_2 is selected from the group consisting of:

-R_4',

-X'-R_4',

-X'-Y'-R_4', and

-X'-R_5';

R_3 is selected from the group consisting of:

-Z-R_4',

-Z-X'-R_4',

-Z-X'-Y'-R_4',

-Z-X'-Y'-X'-Y'-R_4', and

-Z-X'-R_5';

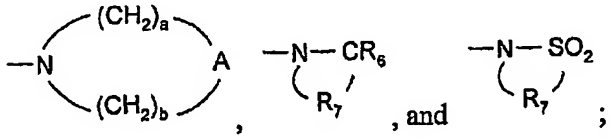
m is 0 or 1 with the proviso that when m is 1 then n is 0 or 1;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy,

halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

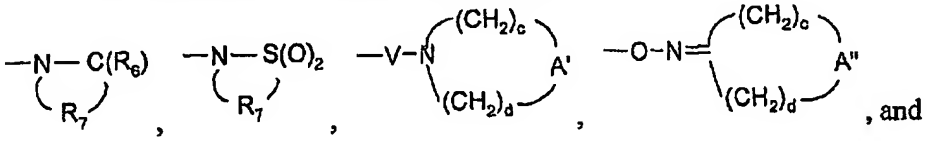
R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

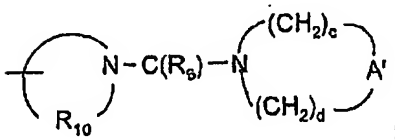


;

R_5' is selected from the group consisting of:



, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A' is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, and $-N(R_4)$-;

A" is selected from the group consisting of -O-, $-S(O)_{0-2}$-, $-N(-Q-R_4)$-, and $-CH_2$-;

Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, $-C(R_6)-S$-, and $-C(R_6)-N(OR_9)$-;

V is selected from the group consisting of $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-O-,

$-S(O)_{0-2}$-,

$-S(O)_2-N(R_8)$-,

$-C(R_6)$-,

$-C(R_6)-O$-,

$-O-C(R_6)$-,

-O-C(O)-O-,

$-N(R_8)-Q$-,

$-C(R_6)-N(R_8)$-,

$-O-C(R_6)-N(R_8)$-,

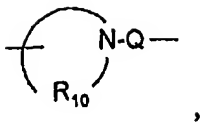
$-C(R_6)-N(OR_9)$-,

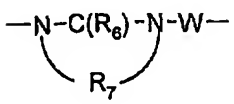
$-O-N(R_8)-Q$-,

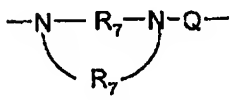
$-O-N=C(R_4)$-,

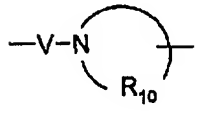
$-C(=N-O-R_8)$-,

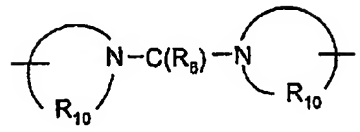
$-CH(-N(-O-R_8)-Q-R_4)$-,


,


,


,


, and

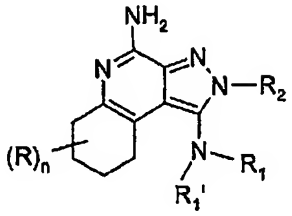

;

Z is a bond or -O-; and

c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7;

or a pharmaceutically acceptable salt thereof.

5. A compound of the Formula V:



V

wherein:

R_1 is selected from the group consisting of:

-R_4,

-Y-R_4,

-X-N(R_8)-Y-R_4,

-X-C(R_6)-N(R_8)-R_4,

-X-O-C(R_6)-N(R_8)-R_4,

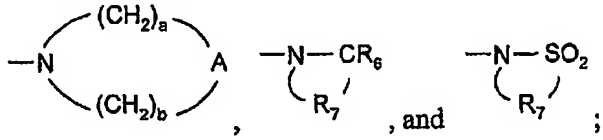
-X-S(O)$_2$-N(R_8)-R_4,

-X-O-R_4, and

-X-R_5;

R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

or R_1 and R_1' together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:

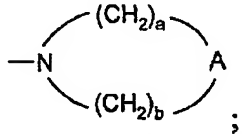


;

A is selected from the group consisting of -CH(R_8)-, -O-, -N(R_8)-, -N(Y-R_4)-, and -N(X-N(R_8)-Y-R_4)-;

X is $C_{2\text{-}20}$ alkylene;

Y is selected from the group consisting of -C(R_6)-, -C(R_6)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_8)-, and -C(R_6)-N(R_{11})-; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group



;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -N(R_8)-, -N(Y-R_4)-, or -N(X-N(R_8)-Y-R_4)- then a and b are independently integers from 2 to 4;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

n is an integer from 0 to 4;

R_2 is selected from the group consisting of:

$-R_4'$,

$-X'-R_4'$,

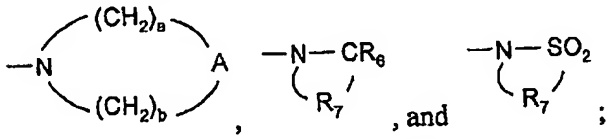
$-X'-Y'-R_4'$, and

$-X'-R_5'$;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

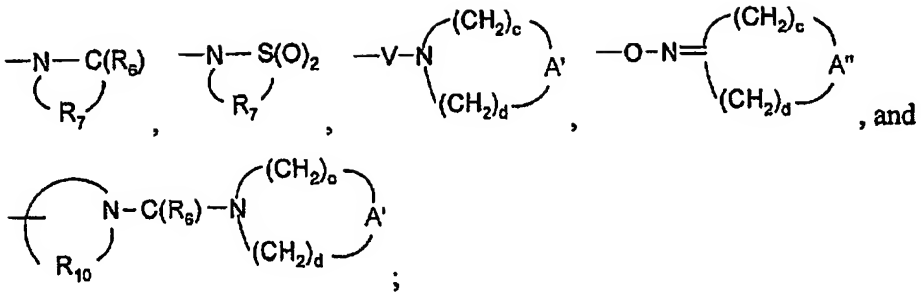
R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



, , and ;

R_5' is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A' is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, and $-N(R_4)$-;

A" is selected from the group consisting of -O-, $-S(O)_{0-2}$-, $-N(-Q-R_4)$-, and $-CH_2$-;

Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, $-C(R_6)-S$-, and $-C(R_6)-N(OR_9)$-;

V is selected from the group consisting of $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-O-,

$-S(O)_{0-2}$-,

$-S(O)_2-N(R_8)$-,

$-C(R_6)$-,

$-C(R_6)-O$-,

$-O-C(R_6)$-,

-O-C(O)-O-,

$-N(R_8)-Q$-,

-C(R6)-N(R8)-,

-O-C(R6)-N(R8)-,

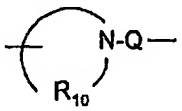
-C(R6)-N(OR9)-,

-O-N(R8)-Q-,

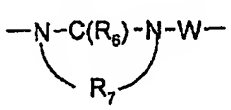
-O-N=C(R4)-,

-C(=N-O-R8)-,

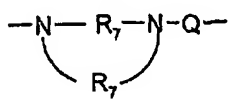
-CH(-N(-O-R8)-Q-R4)-,



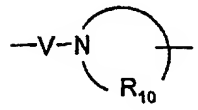
,



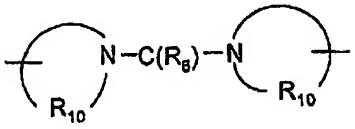
,



,



, and

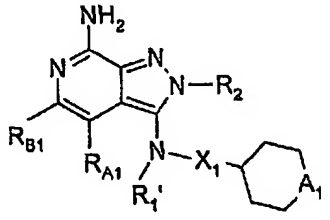


; and

c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7;

or a pharmaceutically acceptable salt thereof.

6. A compound of the Formula XIV:

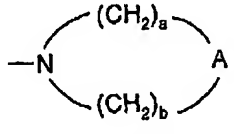


XIV

wherein:

X_1 is a bond or C_{1-4} alkylene;

A_1 is selected from the group consisting of -N(R_8)- and -N(-Y-R_4)-;

Y is selected from the group consisting of -C(R_6)-, -C(R_6)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_8)-, and -C(R_6)-N(R_{11})-; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group  ;

A is selected from the group consisting of -CH(R_8)-, -O-, -N(R_8)-, -N(Y-R_4)-, and -N(X-N(R_8)-Y-R_4)-;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -N(R_8)-, -N(Y-R_4)-, or -N(X-N(R_8)-Y-R_4)- then a and b are independently integers from 2 to 4;

X is C_{2-20} alkylene;

R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
-N(R_9)$_2$;

or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4'$,
$-X'-R_4'$,
$-X'-Y'-R_4'$, and
$-X'-R_5'$;

R_3 is selected from the group consisting of:

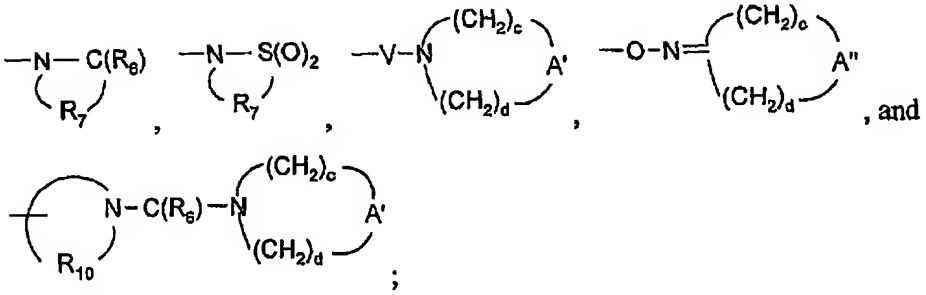
$-Z-R_4'$,
$-Z-X'-R_4'$,
$-Z-X'-Y'-R_4'$,
$-Z-X'-Y'-X'-Y'-R_4'$, and
$-Z-X'-R_5'$;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,

heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5' is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A' is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, and $-N(R_4)$-;

A" is selected from the group consisting of -O-, $-S(O)_{0-2}$-, $-N(-Q-R_4)$-, and $-CH_2$-;

Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, $-C(R_6)-S$-, and $-C(R_6)-N(OR_9)$-;

V is selected from the group consisting of $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and

alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

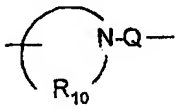
-$C(R_6)$-$N(OR_9)$-,

-O-$N(R_8)$-Q-,

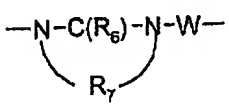
-O-N=$C(R_4)$-,

-C(=N-O-R_8)-,

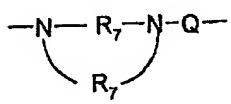
-CH(-N(-O-R_8)-Q-R_4)-,



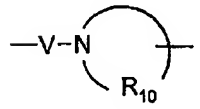
,



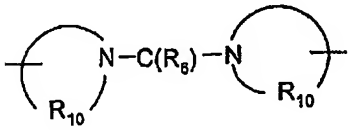
,



,



, and



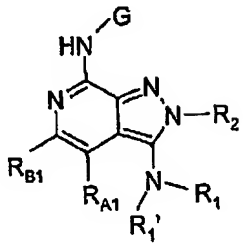
;

Z is a bond or -O-; and

c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7;

or a pharmaceutically acceptable salt thereof.

7. A compound of the Formula XV:



XV

wherein:

G is selected from the group consisting of:

-C(O)-R'",

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R'",

-C(O)-N(R'"")R'",

-C(=NY$_2$)-R'",

-CH(OH)-C(O)-OY$_2$,

-CH(OC$_{1-4}$ alkyl)Y$_0$,

-CH$_2$Y$_1$, and

-CH(CH$_3$)Y$_1$;

R'" and R"" are independently selected from the group consisting of C$_{1-10}$ alkyl, C$_{3-7}$ cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C$_{1-6}$ alkyl, C$_{1-4}$ alkoxy, aryl, heteroaryl, aryl-C$_{1-4}$ alkylenyl, heteroaryl-C$_{1-4}$ alkylenyl, halo-C$_{1-4}$ alkylenyl, halo-C$_{1-4}$ alkoxy, -O-C(O)-CH$_3$, -C(O)-O-CH$_3$, -C(O)-NH$_2$, -O-CH$_2$-C(O)-NH$_2$, -NH$_2$, and –S(O)$_2$-NH$_2$, with the proviso that R"" can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y$_2$ is selected from the group consisting of hydrogen, C$_{1-6}$ alkyl, and benzyl;

Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-*N*,*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl;

Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N*,*N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl;

R_1 is selected from the group consisting of:

-R_4,

-Y-R_4,

-X-N(R_8)-Y-R_4,

-X-C(R_6)-N(R_8)-R_4,

-X-O-C(R_6)-N(R_8)-R_4,

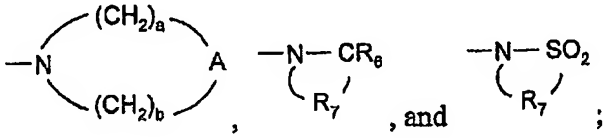
-X-S(O)$_2$-N(R_8)-R_4,

-X-O-R_4, and

-X-R_5;

R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

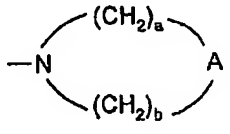
or R_1 and R_1' together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



, , and ;

A is selected from the group consisting of -CH(R_8)-, -O-, -N(R_8)-, -N(Y-R_4)-, and -N(X-N(R_8)-Y-R_4)-;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -C(R_6)-, -C(R_6)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_8)-, and -C(R_6)-N(R_{11})-; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group 

;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -N(R_8)-, -N(Y-R_4)-, or -N(X-N(R_8)-Y-R_4)- then a and b are independently integers from 2 to 4;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
-N(R_9)$_2$;

or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
-N(R_9)$_2$;

R_2 is selected from the group consisting of:

-R_4',
-X'-R_4',
-X'-Y'-R_4', and
-X'-R_5';

R_3 is selected from the group consisting of:

-Z-R_4',

-Z-X'-R_4',

-Z-X'-Y'-R_4',

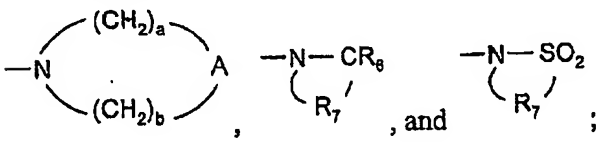
-Z-X'-Y'-X'-Y'-R_4', and

-Z-X'-R_5';

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

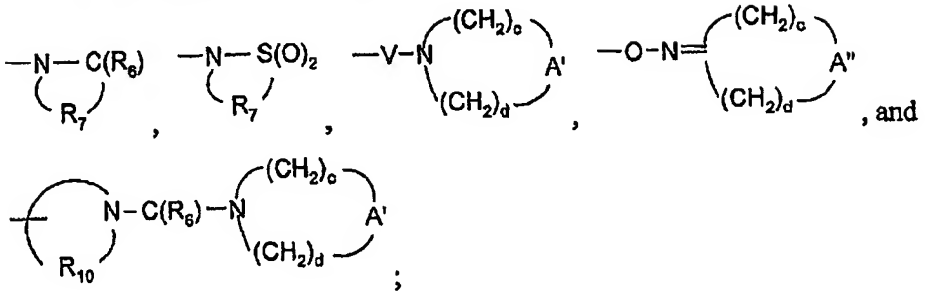
R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



, , and ;

R_5' is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A' is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, and $-N(R_4)$-;

A" is selected from the group consisting of -O-, $-S(O)_{0-2}$-, $-N(-Q-R_4)$-, and $-CH_2$-;

Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, $-C(R_6)-S$-, and $-C(R_6)-N(OR_9)$-;

V is selected from the group consisting of $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-O-,

$-S(O)_{0-2}$-,

$-S(O)_2-N(R_8)$-,

$-C(R_6)$-,

$-C(R_6)-O$-,

$-O-C(R_6)$-,

-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

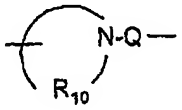
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

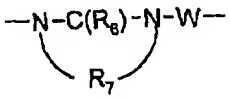
-O-N=C(R_4)-,

-C(=N-O-R_8)-,

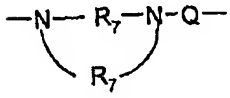
-CH(-N(-O-R_8)-Q-R_4)-,



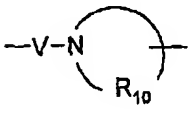
,



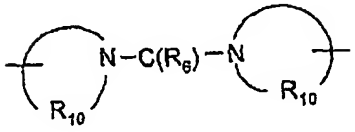
,



,



, and



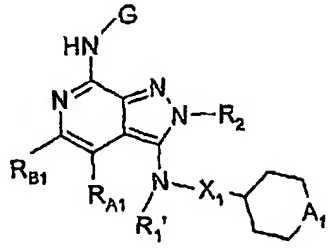
;

Z is a bond or -O-; and

c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7;

or a pharmaceutically acceptable salt thereof.

8. A compound of the Formula XVI:



XVI

wherein:

G is selected from the group consisting of:

-C(O)-R'",

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R'",

-C(O)-N(R'"")R'",

-C(=NY_2)-R'",

-CH(OH)-C(O)-OY_2,

-CH(OC_{1-4} alkyl)Y_0,

-CH_2Y_1, and

-$CH(CH_3)Y_1$;

R'" and R'"" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R'"" can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y_2 is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl;

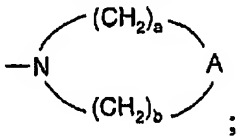
Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-*N*,*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl;

Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N*,*N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl;

X_1 is a bond or C_{1-4} alkylene;

A_1 is selected from the group consisting of -N(R_8)- and -N(-Y-R_4)-;

Y is selected from the group consisting of -C(R_6)-, -C(R_6)-O-, -$S(O)_2$-,

$-S(O)_2-N(R_8)-$, and $-C(R_6)-N(R_{11})-$; wherein R_{11} is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_{11} and R_4 together with the nitrogen atom to which R_{11} is bonded can join to form the group  ;

A is selected from the group consisting of $-CH(R_8)-$, $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, and $-N(X-N(R_8)-Y-R_4)-$;

a and b are independently integers from 1 to 4 with the proviso that when A is $-O-$, $-N(R_8)-$, $-N(Y-R_4)-$, or $-N(X-N(R_8)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

X is C_{2-20} alkylene;

R_1' is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl wherein the alkylenyl group contains at least two carbon atoms between the hydroxy or alkoxy substituent and the nitrogen atom to which R_1' is bonded;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_2 is selected from the group consisting of:
$-R_4'$,
$-X'-R_4'$,
$-X'-Y'-R_4'$, and
$-X'-R_5'$;

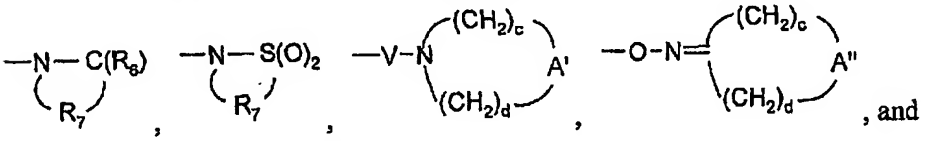
R_3 is selected from the group consisting of:
$-Z-R_4'$,
$-Z-X'-R_4'$,
$-Z-X'-Y'-R_4'$,
$-Z-X'-Y'-X'-Y'-R_4'$, and
$-Z-X'-R_5'$;

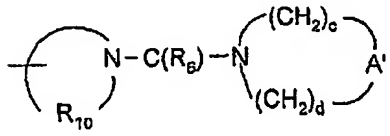
R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_1 is R_4, R_4 is a substituted alkyl group, and the substituent contains a hetero atom which bonds directly to the alkyl group, then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5' is selected from the group consisting of:


, and


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A' is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A" is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-O-,

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

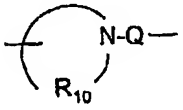
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

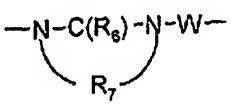
-O-N=C(R_4)-,

-C(=N-O-R_8)-,

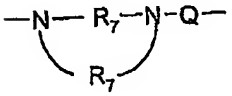
-CH(-N(-O-R_8)-Q-R_4)-,



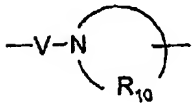
,



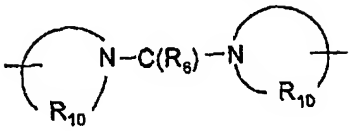
,



,



, and



;

Z is a bond or -O-; and

c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7;

or a pharmaceutically acceptable salt thereof.

9. The compound or salt of claim 1 wherein R_A and R_B are taken together to form a fused aryl ring wherein the ring is a benzo ring which is unsubstituted or substituted by one, two, three, or four R' groups.

10. The compound or salt of claim 3 wherein R_{A2} and R_{B2} are independently hydrogen or C_{1-4} alkyl.

11. The compound or salt of claim 10 wherein R_{A2} and R_{B2} are both methyl.

12. The compound or salt of any one of claims 6, 7, and 8 wherein R_{A1} and R_{B1} are taken together to form a fused aryl ring, wherein the ring is a benzo ring which is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group.

13. The compound or salt of any one of claims 1, 2, 4, and 5 wherein R is hydroxy.

14. The compound or salt of claim 4 or claim 5 wherein n is 0.

15. The compound or salt of claim 4 wherein n is 0 and m is 1.

16. The compound or salt of any one of claims 2, 4, 6, 7, 8, 12, 13 as dependent on claim 4, 14 as dependent on claim 4, or 15 wherein R_3 is selected from the group consisting of phenyl, *p*-tolyl, benzyloxy, (4-chlorobenzyl)oxy, (4-methylbenzyl)oxy, 3-furyl, pyridin-3-yl, 5-(hydroxymethyl)pyridin-3-yl, 6-chloropyridin-3-yl, 6-fluoropyridin-3-yl, 6-methylpyridin-3-yl, 3-quinolin-3-yl, and thiazol-4-ylmethoxy.

17. The compound or salt of any one of claims 4, 13 as dependent on claim 4, or 14 as dependent on claim 4 wherein m is 0.

18. The compound or salt of any one of claims 1 through 5, 7, 9 through 11, 12 as dependent on claim 7, 13, 14, 15, 16 except as dependent on claim 6 or 8, and 17 wherein R_1 is R_4.

19. The compound or salt of claim 18 wherein R_4 is alkyl or arylalkylenyl.

20. The compound or salt of claim 19 wherein R_4 is methyl, ethyl, *n*-propyl, 1-methylethyl, *n*-butyl, 1-ethylpropyl, 2-methylpropyl, 3-methylbutyl, benzyl, 2-phenylethyl, or 3-phenylpropyl.

21. The compound or salt of any one of claims 1 through 5, 7, 9 through 11, 12 as dependent on claim 7, 13, 14, 15, 16 except as dependent on claim 6 or 8, and 17 wherein R_1 is -X-N(R_8)-Y-R_4.

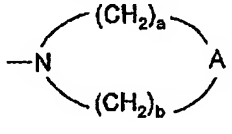
22. The compound or salt of claim 21 wherein X is C_{2-4} alkylene, R_8 is hydrogen, R_4 is C_{1-6} alkyl, Y is -C(O)-, -$S(O)_2$-, or -C(O)-N(R_{11})- wherein R_{11} is hydrogen or R_{11} and R_4 join to form a morpholine ring.

23. The compound or salt of any one of claims 6, 8, and 12 or 16 as dependent on claim 6 or 8 wherein X_1 is C_{1-4} alkylene, and A_1 is -N(R_8)-.

24. The compound or salt of any one of claims 6, 8, and 12 or 16 as dependent on claim 6 or 8 wherein X_1 is C_{1-4} alkylene, and A_1 is -N(-Y-R_4)-.

25. The compound or salt of any one of claims 6, 8, 12 or 16 as dependent on claim 6 or 8, and 24 wherein X_1 is C_{1-4} alkylene, and Y is -C(O)-, -$S(O)_2$-, or -C(O)-N(R_{11})-.

26. The compound or salt of claim 25 wherein R_4 is C_{1-6} alkyl, and R_{11} is hydrogen or methyl.

27. The compound or salt of claim 25 wherein Y is -C(O)-N(R_{11})-, and R_4 and R_{11} form the group 

wherein A is -CH_2- or -O-, and a and b are each independently 1 or 2, with the proviso that when A is -O- then a and b are each 2.

28. The compound or salt of any one of claims 1 through 27 wherein R_1' is hydrogen.

29. The compound or salt of any one of claims 2 through 8, 10, 11, 12, 13 as dependent on claim 2, 4, or 5, 14, 15, 16, 17, 18 through 22 except as dependent on claim 1 or 9, 23, 24, 25, 26, 27, and 28 except as dependent on claim 1 or 9 wherein R_2 is hydrogen, alkyl, alkoxyalkylenyl, or hydroxyalkylenyl.

30. The compound or salt of claim 29 wherein R_2 is C_{1-4} alkyl, C_{1-4} alkyl-O-C_{2-4} alkylenyl, or hydroxyC_{2-4} alkylenyl.

31. The compound or salt of claim 30 wherein R_2 is methyl, ethyl, *n*-propyl, *n*-butyl, 2-methoxyethyl, or 2-hydroxyethyl.

32. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 1-31 in combination with a pharmaceutically acceptable carrier.

33. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of claims 1-31 or the pharmaceutical composition of claim 32 to the animal.

34. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1-31 or the pharmaceutical composition of claim 32 to the animal.

35. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1-31 or the pharmaceutical composition of claim 32 to the animal.